The Journal of Pediatrics

VOL. 50 MARCH, 1957 NO. 3

THE URINARY EXCRETION OF AMINO ACIDS AND SUGARS IN EARLY INFANCY

L. I. WOOLF, PH.D., B.SC., AND A. P. NORMAN, M.D., F.R.C.P.*
LONDON, ENGLAND

THE purpose of this investigation was to determine the changes in the pattern of the amino acids and sugars excreted in the urine of premature and full-term infants from the first day of life until the age of 6 months. It was hoped that the findings might also throw light on the functions of the liver and kidney in early infancy.

In both premature and full-term infants, it was found that changes in the excretion of the individual amino acids occurred with remarkable rapidity. The pattern underwent a number of profound changes before, at the age of about 6 months, it assumed that of the normal older child. A special study was made of amino acid excretion in babies with jaundice, from whatever cause, but no consistent correlation of jaundice with amino-aciduria could be found.

A considerable amount of work on amino acid excretion in infancy has already been done, using paper chromatography and other techniques; but this is the first time a large number of cases over the whole period from birth to 6 months have been investigated by the use of paper chromatography.

Simon[24] found that infants excreted a greater proportion of α-amino nitrogen in the urine than did adults. This was later confirmed by Goebel,[8] Barlow and McCance,[1] Childs,[3] and by Stroder and associates,[31] who also found that premature infants excreted more α-amino nitrogen than did full-term infants.

The estimation of the individual amino acids became possible with the introduction of the techniques of paper chromatography and microbiological assay. Schreier and Plückthun,[22] using the quantitative technique of microbiological assay, estimated eleven amino acids in the blood and urine of premature and full-term infants, older children, and adults. They found that the lysine content of blood was raised in infants as compared with adults and older children, while in premature infants the blood levels of histidine, leucine, valine, phenylalanine, serine, threonine, and tyrosine were also raised.

From The Hospital for Sick Children, Great Ormond Street, and Queen Charlotte's Maternity Hospital.
*Deputy Director, Institute of Child Health, University of London.

Paper chromatography was used by Souchon and his colleagues[26-28] who investigated over 100 infants during the first seven days of life. They found that premature infants excreted a higher proportion of taurine than did full-term infants and greater amounts of all amino acids. In full-term infants the excretion of proline, valine, hydroxyproline, methionine, and glycine rose during the first seven days of life, while that of taurine and cystine fell. Bickel[2] obtained similar results in a smaller series, as did Morton and co-workers.[19]

Lo Bianco,[15] using the same method, investigated a number of premature and full-term infants in the first year of life, classifying them in three-month age groups. Lo Bianco,[15] Souchon,[26] and Jonxis[12, 13] found qualitative and quantitative differences between the amino acids excreted by babies fed on cow's milk and those fed on breast milk. Jonxis,[13] and Stroder and associates[31] noted that the total amino acid excretion in premature infants rose to a maximum on the second, third, or fourth day of life, and then fell till the tenth day.

More recently Sereni and collaborators,[23] have examined the clearances of seventeen amino acids in premature and full-term infants, children, and adults, using paper chromatography for determining amino acid levels in blood and urine. Comparing these with creatinine clearance, they concluded that both glomerular filtration rate and tubular reabsorption of amino acids were decreased in premature infants.

The second quantitative technique, chromatography on columns of ion-exchange resins, has been applied by Dustin, and associates[6] in the estimation of almost all the amino acids present in urine. Their estimations were done on two twenty-four-hour specimens of urine from a premature infant, one from a full-term infant, and one from an adult. They found that the full-term infant excreted considerably larger amounts of amino acids than the adult, while the premature infant excreted more still. The greatest differences occurred in the excretion of proline, tyrosine, glycine, threonine, alanine, valine, leucine, and isoleucine.

MATERIALS AND METHODS

The urine was collected chiefly from male infants born in Queen Charlotte's Maternity Hospital; specimens were also received from the obstetric department of Hillingdon Hospital, and from the premature baby unit of Hammersmith Hospital. There was no selection, either of the normal full-term infants or of the premature babies, except that an attempt was made to include as many small premature infants and as many infants showing severe jaundice as possible. This attempt was hindered by the fact that the babies were often too feeble or too ill for even a minor disturbance to seem justifiable. The choice of male, and not female, infants was simply determined by the ease with which urine could be collected from the former. The specimen was obtained in some instances by using a special collecting funnel[2a] but for the most part a small test tube was found easier to use. This was strapped on with "Sleek" adhesive plaster, which was found to cause little or no damage to the skin.

Consecutive specimens from the same child at intervals of one day were obtained whenever possible during the first ten days of life, but the majority of specimens were isolated collections from different children and seldom amounted to more than three or four from any one child.

The specimen of urine, preserved with chloroform or chlorbutol,* was placed in a refrigerator immediately after collection. Urines from those older infants who had returned home were delivered by hand or by post in jars containing a little chlorbutol, so that there was sometimes a delay of about twenty-four hours before they were placed in a refrigerator.

Blood.—Blood for serum amino acid estimation was, as a rule, collected by heel prick, although sometimes by venepuncture. The time of collection bore no set relation to feedings. A specimen of urine was obtained from the child on the same day as the specimen of blood in order that comparison might be made of the amino acid contents of the two fluids.

Technique.—The technique of paper chromatography used was that described by Woolf[32] which was in turn based on that described by Consden and associates.[5] In this method the variable concentration of the urine is offset by measuring the concentration of creatinine in the specimen. The daily excretion of creatinine is approximately constant for any one individual[21]; hence, a volume of urine containing a given amount of creatinine will represent a fixed proportion of its daily excretion. It was found[32] that in more dilute specimens of urine the proportion of amino acids to creatinine was higher than in more concentrated specimens. A volume of urine, calculated from the formula $V = 7.15\ C^{-2/3}$, where V is volume in milliliters, and C is creatinine concentration in milligrams per 100 ml., gave more constant results for normal individuals, and this "calculated volume" was used for investigating the urine of these infants. For the purpose of this investigation, it was assumed that the same relationship held true in the newborn infant. The amount of each amino acid present in the calculated volume of a given specimen of urine was estimated by visual comparison of the chromatograms with a series of standard sheets. These sheets were prepared from a solution containing known amounts of amino acids.

The urinary creatinine was determined by the Jaffe reaction, using a photoelectric colorimeter with an Ilford 603 filter (max. $\gamma = 490\ m\mu$).

For investigation of blood amino acids the serum was in most cases passed through a column of acid-form Zeo-Karb 225 (sulfonated polystyrene beads, approximately 12 per cent crosslinked, about 0.5 mm. diameter). Proteins, acid and neutral substances were washed away, then the amino acids were desorbed with 5M-ammonia. The eluate was taken to dryness in vacuo, made up to volume, and examined by paper chromatography. There resulted very clear paper chromatograms of all the amines and amino acids except taurine, which is not adsorbed by the resin, and β-aminoethyl phosphoric ester which is only partially adsorbed. In order to demonstrate taurine, in five specimens of serum, the older method of protein precipitation with trichloroacetic acid was employed, followed by extraction of excess trichloroacetic acid with ether and then electrolytic desalting, before paper chromatography.

Conjugated amino acids were investigated in specimens of urine from two infants and two adults to provide a direct comparison. The urine was passed through a Zeo-Karb 225 column as described above, then the unadsorbed material (effluent and washings) was passed through a column of Deacidite H (a weak-base resin containing dimethylamine groups, in the form of beads about 0.5 mm. diameter). The original urine, the ammonia eluate from the first column, the hydrochloric acid eluate from the second column, and the effluent and washings that had passed through both columns (i.e., unadsorbed material) were hydrolyzed (6N hydrochloric acid, 105° C., 16 hours) and examined by two-dimensional paper chromatography together with the unhydrolyzed materials. Specimens of urine from seven other infants were hydrolyzed

*Chlorbutol = 2-trichloromethylpropan-2-ol.

and the amino acids examined by paper chromatography, together with the unhydrolyzed urines.

In order to demonstrate ethanolamine, a specimen of urine was passed through a Zeo-Karb 225 column which was washed, then treated with 5M-ammonia, and the eluate taken to dryness in vacuo. The residue was taken up in water and passed through a column of Amberlite IRA-400 in the hydroxide form (a bead-form, strong-base resin containing quaternary ammonium hydroxide groups); the unadsorbed material in the effluent, and the acetic acid eluate, from the second column, were examined by paper chromatography. The effluent and washings from the Amberlite IRA-400 were passed through a column of Zeo-Karb 226 (a bead-form, weak-acid resin containing carboxyl groups); the effluent and ammonia eluate were examined by paper chromatography.

Paper chromatography was also used in the examination of sugars,[32, 33] as no other method is sufficiently sensitive to detect the small amounts present, nor will any other simple method distinguish one sugar from another. The concentration of each sugar was estimated by visual comparison of the spots produced with those of known amounts of sugars on the same chromatogram.

RESULTS

In each amino acid chromatogram two factors have to be considered: the amount of each amino acid present, as indicated by the size and intensity of the spot it forms, and the pattern (i.e., the amounts, relative one to another, of all the amino acids present) (Figs. 9 to 14). Figs. 1 to 7 show the amounts found of each of seven substances.

In order to avoid any undue weighting, when more than one specimen of urine was collected from a child in a period of time represented by a single column, only the middle specimen (if an odd number of specimens were collected) or the one past the middle (if even) is shown on the diagram. For this reason the results obtained for sixteen specimens of urine are not recorded on the diagrams. These sixteen specimens, with one exception, gave chromatogram patterns and contained amounts of the different amino acids and creatinine very similar to those in the other specimens collected from the same children during the same period. Within the period represented by a single column the variation from specimen to specimen for a given child was much less than the variation from child to child. The single exception was provided by the specimen passed by infant 2 on the twenty-third day of life, which is not recorded on the diagrams: this contained 30 μg of lysine, 50 μg of proline, 50 μg of hydroxyproline, 30 μg of taurine, and 5 μg of ethanolamine in the calculated volume (2.26 ml.), while that on the thirtieth day, recorded on the diagrams, contained 50 μg of lysine, 100 μg of proline, 100 μg of hydroxyproline, over 100 μg of taurine, and over 42 μg of ethanolamine in the calculated volume (2.00 ml.).

The method of estimation of an amino acid, etc., is not exact and the amounts shown in Figs. 1 to 6 are orders of magnitude rather than accurately measured quantities. These amounts are those present in the calculated volume of urine V, where $V = 7.15\ C^{-2/3}$ ml., C being the creatinine concentration in milligrams per 100 ml.

In addition to the seven substances represented in Figs. 1 to 7, many other substances detected on the

chromatograms were excreted in amounts differing from those seen in normal older children.

Leucine and Isoleucine.—Very little leucine and isoleucine were excreted during the first two or three days of life. The amount present in the urine then rose to about twice the maximum seen in healthy older children, but never approached the levels found in children with diseases involving renal tubular reabsorptive failure, or with hepatic dysfunction. The average concentration of leucine together with isoleucine was 3.5 μg in the calculated volume, compared with 2 μg for older children. The smaller premature infants excreted more, up to 20 μg.

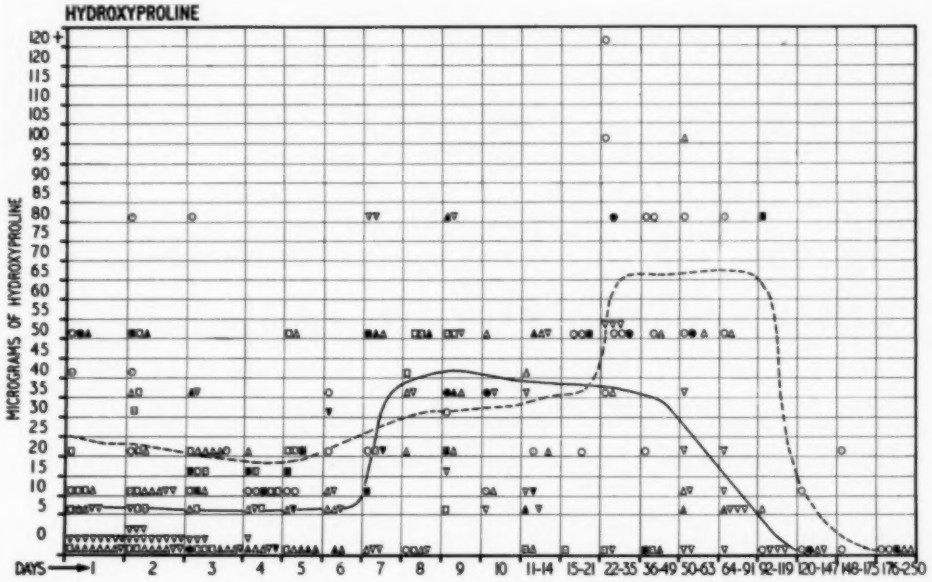
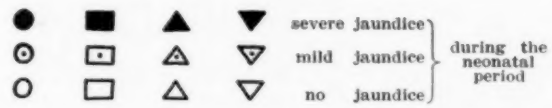


Fig. 1.—Hydroxyproline excretion. The normal older child excretes an average of 4 μg of hydroxyproline in the calculated volume.

Figs. 1 to 7.—Each point represents a single specimen of urine; the ordinate gives the amount of the amino acid present in a volume of the urine calculated from the creatinine content, the abscissa the age of the infant when the specimen was collected. Neither the ordinate nor the abscissa scale is continuous; thus, all specimens falling in the "O" rank contain no detectable amount of the amino acid in question, and a specimen falling in the column for any one day could have been collected at any time on that day. This applies to columns for groups of days also. The sign "+" indicates that these specimens contained more than the largest amount of the amino acid that could be estimated on the chromatogram with any accuracy. The different symbols indicate the birth weight and clinical condition of the infant from whom the urine was collected:

Birth Weight: 0-1.8 1.8-2.5 2.5-3.4 >3.4 kilograms



The mean excretion for infants of over 2.5 kilogram birth weight, during each day or group of days represented by a single column, was calculated and a smoothed curve drawn through the means (———). This was also done for infants of birth weight under 2.5 kilograms (------).

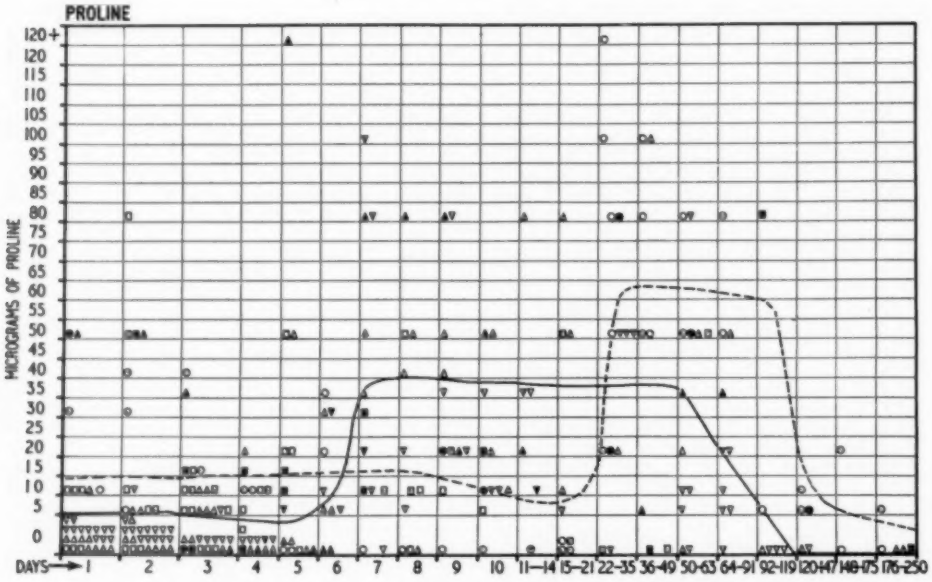


Fig. 2.—Proline excretion. The normal older child excretes no detectable proline (<2 μg in the calculated volume).

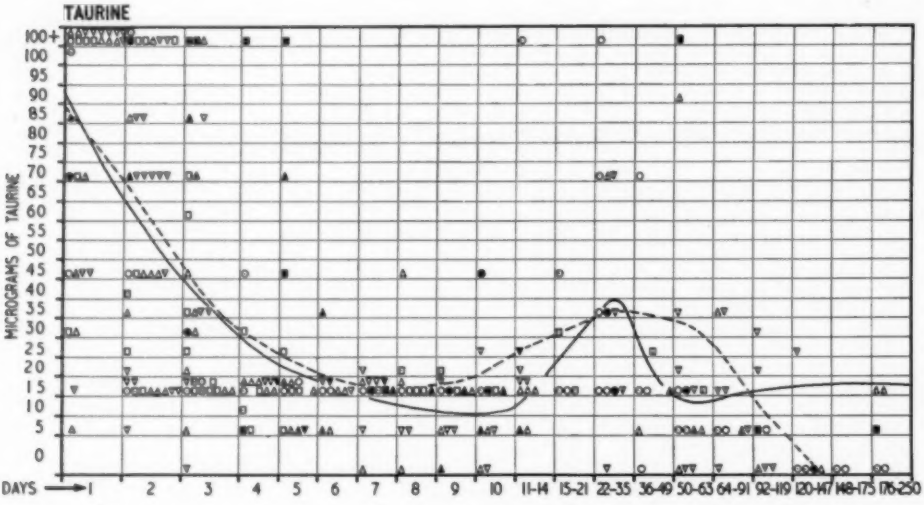


Fig. 3.—Taurine excretion. Normal children aged from 1 to 12 years excrete, on the average, 15 μg of taurine in the calculated volume, but there is a moderate steady rise with age.

Valine.—Valine resembled leucine plus isoleucine closely in each specimen of urine.

Lysine.—Most specimens of urine from older children contain between 0 and 7 μg of lysine in the calculated volume.

There was a marked tendency for the amount of lysine to be fairly constant in all the specimens passed by a given infant. Of the forty-eight specimens containing not less than 30 μg of lysine in the calculated volume, thirty-one were produced by a group

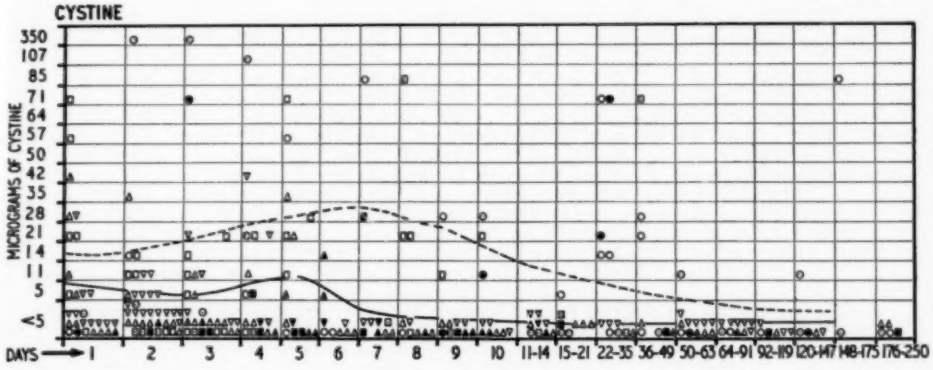


Fig. 4.—Cystine excretion. The two specimens (both from infant 1) with 350 μg of cystine were excluded when calculating the means. It is difficult to estimate small amounts (<5 μg) of cystine accurately. Normal older children excrete <5 μg of cystine in the calculated volume.

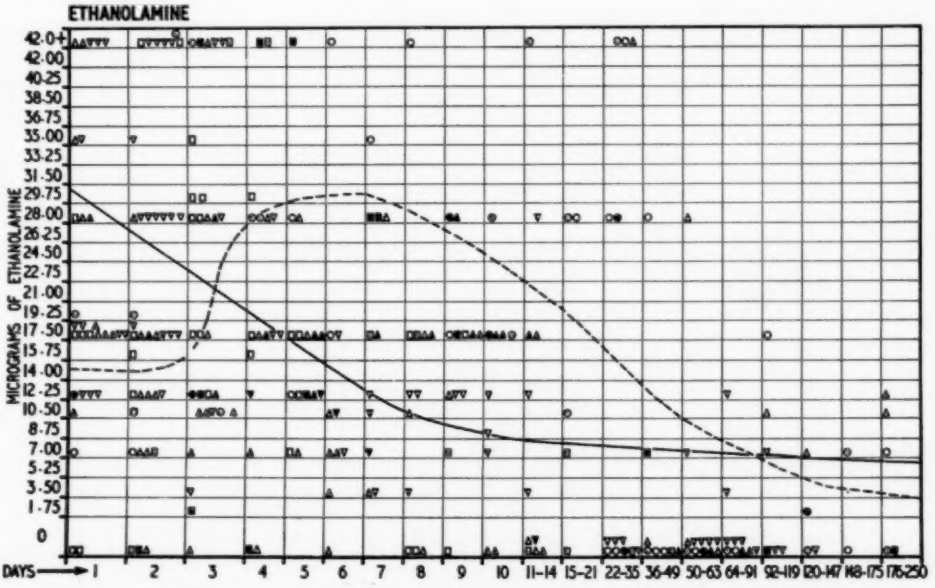


Fig. 5.—Ethanolamine excretion. The normal older child excretes 7 μg of ethanolamine in the standard volume.

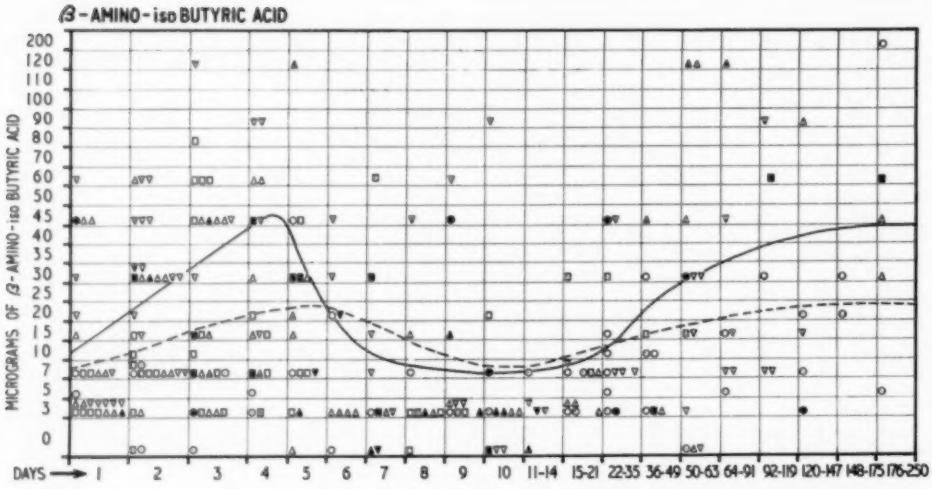


Fig. 6.—β-Amino-isobutyric acid excretion. There is considerable variation among older children in their excretion of β-amino-isobutyric acid, but on the average there is 10 μg in the calculated volume.

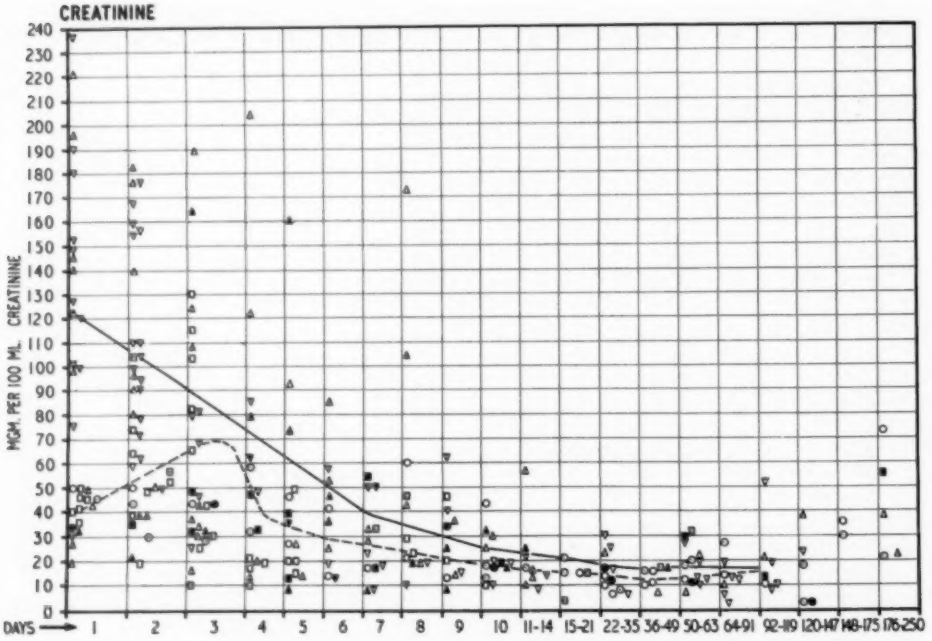


Fig. 7.—Creatinine concentration of urine. The ordinate shows the concentration of creatinine (in milligrams per 100 ml.) in each specimen of urine.

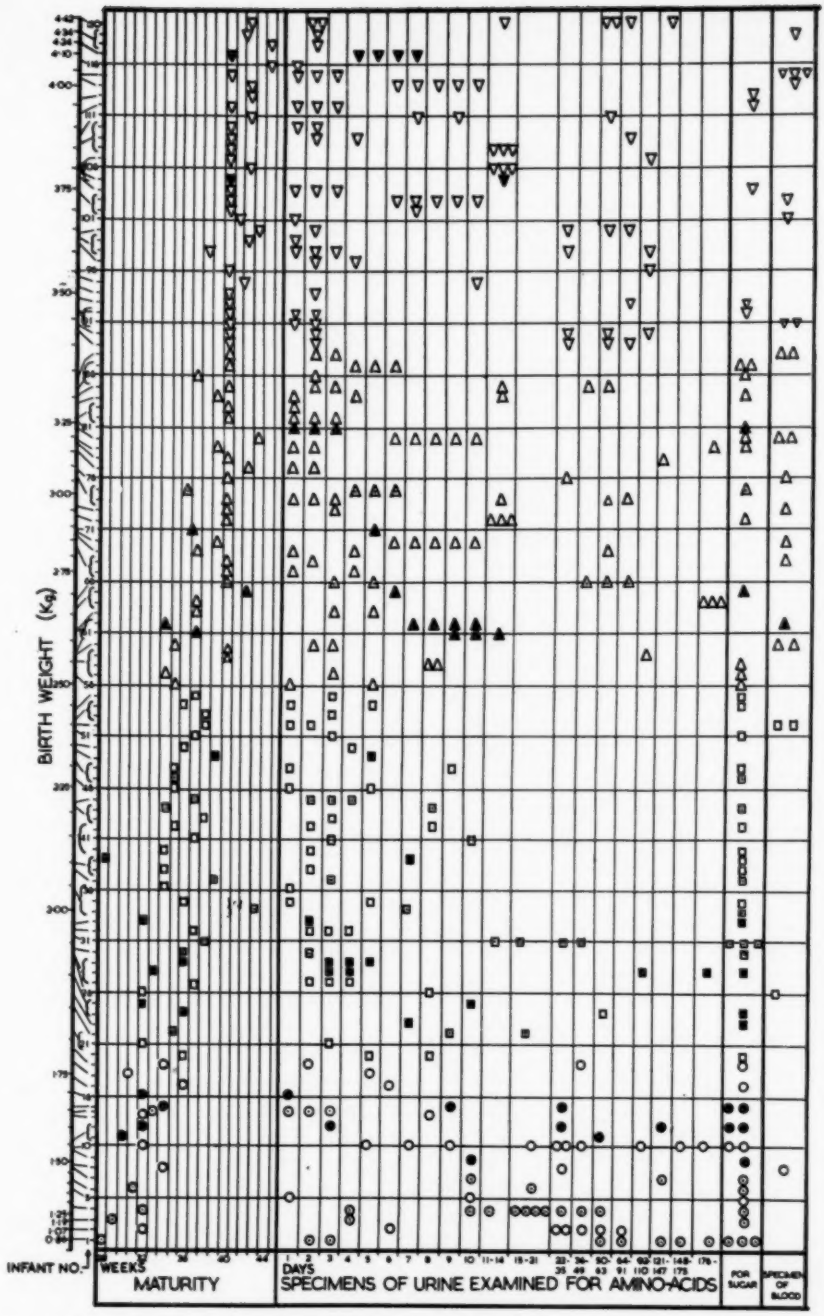


Fig. 8.—Details of the infants investigated, showing, on the left, birth weight, maturity (period of gestation) where known, and degree of jaundice. Symbols as in Fig. 1.

The number of specimens of urine, from each child, that were examined for amino acids, and the days on which they were collected, are shown in adjoining compartments, each point representing a single specimen. The next two compartments show the number of urine specimens examined for sugars, and the number of specimens of blood examined for amino acids. Specimens of fetal urine and cord blood are not shown.

of eight infants who between them produced only three specimens with less than 30 μg of lysine. Of the other seventeen specimens, ten were the only ones examined from the infant in question, and five were passed on the first day of life by infants whose subsequent specimens were low in lysine.

TABLE I. LYSINE EXCRETION

LYSINE (μG IN THE CALCULATED VOL.)	BIRTH WEIGHT (KG.)				
	0-1.8	1.8-2.5	2.5-3.4	OVER 3.4	TOTAL
	NUMBER OF SPECIMENS OF URINE				
0-7	29	29	56	54	168
8-29	9	8	8	8	33
30-80	12	6	9	11	38
81-180	2	2	1	3	8
240	2	0	0	0	2
Total	54	45	74	76	249

There was some evidence that lysine excretion varied with age, but not in a regular manner. Thus five infants excreted large amounts of lysine on the first day of life but not subsequently. Infant 1 excreted 240 μg of lysine in the calculated volume on the second and third days of life and 30, 60, and 75 μg, respectively, at 7 weeks, 3 months, and 4 months, but only 3 μg at 5½ months and none at 7 months. No other infant excreting large amounts of lysine was followed long enough to see whether a similar drop occurred.

About half the specimens containing more than 20 μg of lysine in the calculated volume also contained increased amounts of cystine, the two amino acids often being raised to a similar extent in a given specimen.

Most of the specimens of blood examined contained markedly increased amounts of lysine (Table IV), though the corresponding urine specimens generally contained no more than the normal traces of lysine. No correlation could be discovered between blood and urinary lysine levels. Two of the infants passed urine high in lysine on the same day as a specimen of blood was obtained; the blood of one of these infants contained no detectable lysine (urinary lysine 150 μg, urinary cystine 100 μg), while that of the other infant contained about 2.5 mg. per 100 ml. serum (urinary lysine 60 μg, urinary cystine under 7 μg).

Glycine.—The amounts of glycine present in infants' urine were considerably greater than those found in the urine of older children.

Unidentified Substance 1.—This substance gives a well-rounded, reddish purple spot with ninhydrin and runs to a position under hydroxyproline almost coincident with that of α-aminobutyric acid. It resists hydrolysis with 6N hydrochloric acid at 105° C. for 4 hours, but vanishes after 16 hours' hydrolysis. It is adsorbed by Zeo-Karb 225 and desorbed by ammonia. It is present in much smaller amounts in urine from older children.

Unidentified Substance 2.—This gives a gray spot over ethanolamine. Histamine gives a spot of similar color, but different R_F* values. Substance 2 is present in considerable amounts in many infants' urine, but is never seen in that of older children.

Unidentified Substances 3 and 4.—These give elongated, blue-purple spots of high R_F value in cresol-ammonia and low R_F value in collidine-lutidine. They are adsorbed by Zeo-Karb 225 (and the carboxylic resin, Zeo-Karb 226), and desorbed by ammonia, but are not adsorbed by Am-

*The R_F value[5] of a substance is the distance it moves on a paper chromatogram relative to the distance moved by the solvent front. The R_F value of a substance in a given solvent is a physical constant characteristic of that substance.

berlite IRA-400 (OH form). Hence, they are bases and lack carboxyl or other acid groups. Cadaverine and putrescine give similar spots of the same R_F values and behave similarly with ion-exchange resins.

They are most in evidence on the first day of life. Similar spots are seen less frequently in urine from older children.

Unidentified Substance 5.—A substance giving a brown spot is present in many infants' urine, particularly after the ninth day of life. Carnosine gives a similar spot in the same position. Like carnosine, the substance is acid-labile. A similar spot of the same size is seen in urine from older children.

TABLE II. TYROSINE EXCRETION

TYROSINE (μG IN THE CALCULATED VOL.)	BIRTH WEIGHT (KG.)				
	0-1.8	1.8-2.5	2.5-3.4	OVER 3.4	TOTAL
	NUMBER OF SPECIMENS OF URINE				
0-8	34	36	75	72	217
9-19	5	6	2	2	15
20-49	8	4	2	0	14
50-100	7	0	0	0	7
Total	54	46	79	74	253

Identification of Ethanolamine.—In two specimens of urine the substance reacting with ninhydrin and running to the position of ethanolamine was found in the unadsorbed effluent from the Amberlite IRA-400 column in the same amount as was originally present in the urine. There was no trace of it in the acetic acid eluate. It was present in the ammonia eluate from the carboxylic resin Zeo-Karb 226, but not in the unadsorbed effluent.

Hence, the substance is adsorbed by both strong and weak acid resins and desorbed from both by ammonia. It is completely unadsorbed by the strong-base resin. It follows that it is a base comparable in strength to lysine and histidine, and that it contains no carboxyl or other acid group. Ethanolamine behaves in just this fashion with ion-exchange resins.

The substance in urine reacted with ninhydrin at a rate similar to that of ethanolamine and gave a spot of the same color. It resisted acid hydrolysis and oxidation with hydrogen peroxide containing molybdate. When ethanolamine was added to a specimen of urine, no separation occurred on columns of different ion-exchange resins, and no extra spot appeared on the paper chromatogram, but the spot due to the substance increased in intensity.

Identification of β-Amino-Isobutyric acid.—A substance occurs in many of these specimens which, on a two-dimensional paper chromatogram, takes up a position which cannot be distinguished by eye from that taken up by β-amino-isobutyric acid, sarcosine, and methionine sulfoxide. This substance is identified as β-amino-isobutyric acid on the following evidence.

The substance and β-amino-isobutyric acid both react similarly with ninhydrin, whereas sarcosine reacts much more slowly and gives a slightly redder spot. Methionine sulfoxide is oxidized by hydrogen perioxide and molybdate to methionine sulfone, which gives a spot in a different position on the paper chromatogram, while the substance is unchanged by hydrogen peroxide treatment, as in β-amino-isobutyric acid. The spot due to the substance increases in intensity but remains single when synthetic β-amino-isobutyric acid is added to urine, but when sarcosine is added the

change in size and shape indicates the presence of two overlapping spots.

The substance in urine and β-amino-isobutyric acid are similarly adsorbed by and desorbed from the strong acid resin Zeo-Karb 225, and the strong-base resin Amberlite IRA-400. Neither is adsorbed by the weak-base resin Deacidite H. After adsorption on the weak acid resin, Zeo-Karb 226, they are eluted before the basic amino acids, but after all the other α-amino-acids, including sarcosine; in this they resemble other ω-amino-acids.

The substance resists hydrolysis with 6N hydrochloric acid for 16 hours at 105° C., indicating it is not a peptide.

Identification of Taurine.—Apart from its unique position on a paper chromatogram, taurine is the only substance known to occur in urine that gives a strong blue-purple spot with ninhydrin and is completely unadsorbed by the strong acid resin, Zeo-Karb 225, under the conditions used by us. Taurine is adsorbed by the weak-base resin, Deacidite H, but is rapidly eluted by aqueous carbonic acid, unlike for example, diglycylglycine or cysteic acid, which require stronger acids.

The taurine in a specimen of urine could not be separated from added taurine when the mixture was passed through columns of different resins, eluted by different techniques, and submitted to paper chromatography.

The taurine in urine resisted acid hydrolysis and oxidation with hydrogen peroxide containing molybdate.

Conjugated Amino Acids.—Ten specimens of urine from nine infants were examined. All contained conjugated amino acids, released on acid hydrolysis, comparable in amount to the conjugated amino acids of adult urine. In the urine of infant 90, passed on the second day of life, of infant 84, passed on the third day of life, and of two adults, about a quarter* of the total conjugated amino acids were adsorbed by Zeo-Karb 225 and eluted by ammonia. In all four the conjugated amino acids adsorbed by Zeo-Karb 225 released, on hydrolysis, considerable amounts of proline and hydroxyproline, and a trace of taurine (identified as above), although no free taurine was retained by the Zeo-Karb 225 and three of the urines contained no free proline or hydroxyproline. The other conjugated amino acids retained by Zeo-Karb 225 included much leucine, valine, alanine, glycine, lysine, glutamic acid, histidine, and smaller amounts of tyrosine and β-alanine.

In all four specimens the only free amino acids adsorbed by the Deacidite H column were taurine and some phosphoryl-ethanolamine. On acid hydrolysis large amounts of glycine and glutamic acid, much smaller amounts of aspartic acid, and traces of other amino acids, including β-alanine and ethanolamine, were released. It has been found that N-acylated amino acids, such as hippuric acid, phenylacetylglutamine, pantothenic acid, acetylglycine, acetylmethionine, and acetyltryptophan are adsorbed by Deacidite H, but not by Zeo-Karb 225, under the conditions used by us.

In none of the four urines did the material adsorbed by neither the strong-acid nor the weak-base resin contain any free amino acids or peptides reacting with ninhydrin. This fraction contained rather less than

*The relative amounts in the different fractions could only be roughly estimated.

half the total amount of conjugated amino acids in each urine. The main amino acids released on hydrolysis were glycine, glutamic acid, aspartic acid, alanine, leucine, valine, and proline. There were smaller amounts of hydroxyproline, β-alanine, lysine, tyrosine, arginine, phenylalanine, serine, threonine, and γ-amino-butyric acid.

Sugars.—No correlation was detected in this series between birth weight or clinical condition on the one hand and excretion of sugars on the other. Nor was there, after the first three days, any correlation between age and sugar excretion.

Four* out of the eight specimens passed on the first day of life contained between 4 and 10 mg. of glucose per 100 ml. of urine. The other four contained no detectable glucose. Six out of the eleven specimens passed on the second and third days of life contained 3 to 10 mg. of glucose per 100 ml., the other five containing none. Of these nineteen specimens only three contained any detectable lactose, while only seven contained galactose (from 5 to 10 mg. per 100 ml.). By the fourth day more specimens contained lactose and galactose.

There was a moderately high correlation between the amounts of lactose and of galactose in a specimen of urine, but little correlation between the excretion of these sugars and the amount of glucose present.

*From infants 5, 103, 111, 112.

In respect to other sugars, a few specimens of urine contained small amounts of sucrose (up to 25 mg. per 100 ml.) and fructose (up to 8 mg. per 100 ml.), such as are frequently found in the urine of older children. Seven infants passed specimens of urine containing substances with R_F values and color reactions of arabinose (up to 15 mg. per 100 ml.) and xylose (up to 5 mg. per 100 ml.)* No correlation could be discovered between these pentoses and the other sugars present.

The effects of large amounts of sucrose in the diet were shown by two infants. Infant 1 excreted large amounts of fructose, sucrose, and glucose while on a sweetened condensed milk feeding; at 7 weeks he excreted 70 mg. of fructose, 27 mg. of sucrose, and 20 mg. of glucose per 100 ml., while at 3 months he excreted 150 mg. fructose, 25 mg. sucrose, and 150 mg. glucose per 100 ml.; when he was fed less sucrose these sugars vanished from the urine.

Infant 46 excreted 100 mg. of sucrose per 100 ml. urine on the third day of life while being fed a sucrose-containing formula; his urine contained 10 mg. glucose, 10 mg. galactose, and 40 mg. lactose per 100 ml., but no fructose.

Protein.—On testing with salicyl-sulfonic acid, none of the urines in

TABLE III. EXCRETION OF SUGARS

SUGAR	CONCENTRATION (MG./100 ML.) NUMBER OF SPECIMENS						
	0	1-4	5-9	10-19	20-39	40-80	>80
Galactose	18	4	13	13	7	5	0
Glucose	33	5	11	8	2	0	1
Lactose	34	2	0	5	7	6	6

*Three of these specimens were passed by infants 103, 111, and 112, on the first day of life; the others were passed on the second, third, fifth, and eighth days of life, respectively, by infants 29, 54, 34, and 57.

this series revealed the presence of protein in amount exceeding 20 mg. per 100 ml.

Serum Amino Acids.—The amino acids were investigated in twenty-four specimens of serum from seventeen infants and proved very similar in amount and distribution to those in older children and adults. Too few specimens were obtained from the smaller premature infants to permit comparing them with full-term infants. The serum resembled that of older children in its proline content, both during the first few days of life, when proline was absent from the serum. There was rather more β-amino-isobutyric acid than in serum from older children and adults.

The taurine content of the five specimens examined lay between 0 and 2 mg. per 100 ml. serum. This is the same range of values as is found in older children. In a specimen of serum obtained on the first day of life, from infant 114, the taurine content was 1 mg. per 100 ml., but a specimen of urine also obtained on the first day contained over 100 μg of taurine in the calculated volume. A similar combination of low serum taurine (2 mg. per 100 ml.) and high urinary taurine (70 μg) held for infant 75 on the twenty-third day of life.

TABLE IV. THE LYSINE CONTENT OF BLOOD SERUM

	DAY OF LIFE					
	1	2	3	6-10	22-35	TOTAL
LYSINE (MG./100 ML.)	NUMBER OF SPECIMENS					
20-25	3	1				4
10-19		3				3
5-9		1		3	1	5
2-4		2	2	2		6
<2	1		2	2	1	6
Total	4	7	4	7	2	24

urine, and later, when proline was being excreted in large amounts. The greatest difference was in the increased amount of lysine present.

On the first day of life this was as much as 25 mg. per 100 ml., whereas in older children the serum lysine content is usually below 2 mg. per 100 ml. A sharp decline in lysine content during the first three days of life was noticeable in consecutive specimens of blood from three infants.

Small amounts of ethanolamine were detected in twelve specimens. Traces of hydroxyproline, about 250 μg per 100 ml. of serum, which is on the borderline of detectability, were seen in three. These substances are never seen in serum from normal older children, using the same volume of

Fetal Urine.—Specimens of the urine passed a few seconds after birth were obtained from six normal full-term infants. It is possible that a proportion of the urine may have been secreted during labor and the contents modified by the process of birth.

They were all very dilute (creatinine 4 to 12 mg. per 100 ml.) and free from protein. All contained traces of glucose (from 0.5 to 3 mg. per 100 ml.) and fructose (up to 1 mg. per 100 ml.), and four contained lactose (up to 1½ mg. per 100 ml.), while one appeared to contain mannose (about 5 mg. per 100 ml.). The mannose was identified by its R_F value (compared

Figs. 9 to 14.—Paper chromatograms of urinary amino acids. In each chromatogram the urine was applied at the point marked +; p-cresol was run from right to left, then a lutidine-collidine mixture from top to bottom. The spot due to proline is marked "P," that due to hydroxyproline "HP," and that due to unidentified substance 5 is marked "ANS"; these spots, differing in color from the others, are partially outlined with dotted lines.

Fig. 9.—A typical normal full-term infant (No. 78) on the first day of life. As well as taurine and ethanolamine, lysine and cystine are present in large amounts.

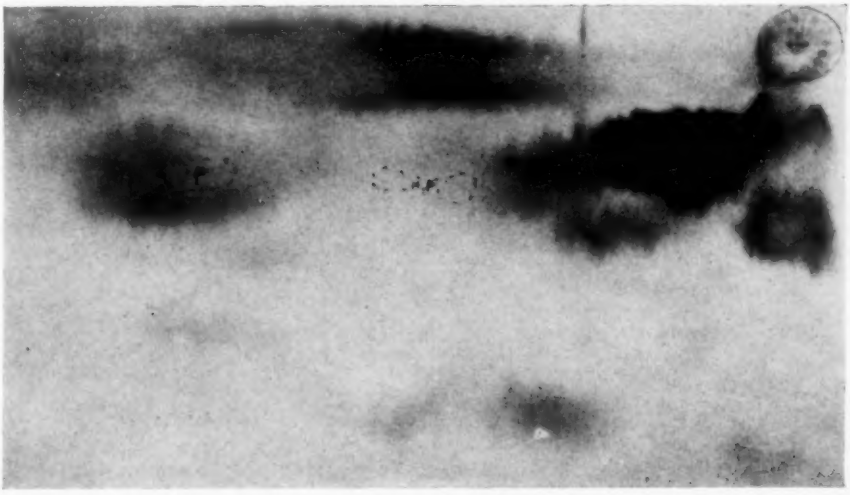


Fig. 10.—A very small premature infant (No. 1) on the second day of life. The volume used is one-quarter the calculated volume, to avoid grossly overloading the chromatogram.

with an authentic specimen run alongside), the color it gave with aniline phthalate, and its failure to give a red color with naphthoresorcinol.

Fig. 11.—A normal full-term infant (No. 107) on the eleventh day of life. Excretion of proline and hydroxyproline has reached its peak.

Fig. 12.—A premature infant (No. 10) on the eighteenth day of life. Proline has not yet appeared, while ethanolamine excretion is still high.

The specimens resembled one another closely in their amino acid content. Taurine was very prominent in all (from 70 to 120 μg in the calculated volume) while lysine was even more prominent in all but one specimen (from 120 to 200 μg). Ethanolamine (15 to 50 μg) was also prominent in all the specimens. Glycine was prominent in two specimens and β-amino-isobutyric acid in four specimens. Proline and hydroxyproline were present in small amounts (1 to 5 μg) in all but one specimen. The other amino acids, etc., were not very different in amount from those of most

newborn children; unidentified substance 2 was present in one specimen.

Fetal Blood.—Specimens of blood were obtained from the umbilical cord of ten full-term infants, one infant of 38 weeks' maturity but 3.33 kilogram birth weight, and one postmature child of 43 weeks. One mother had had mild toxemia during pregnancy; otherwise all the mothers and infants

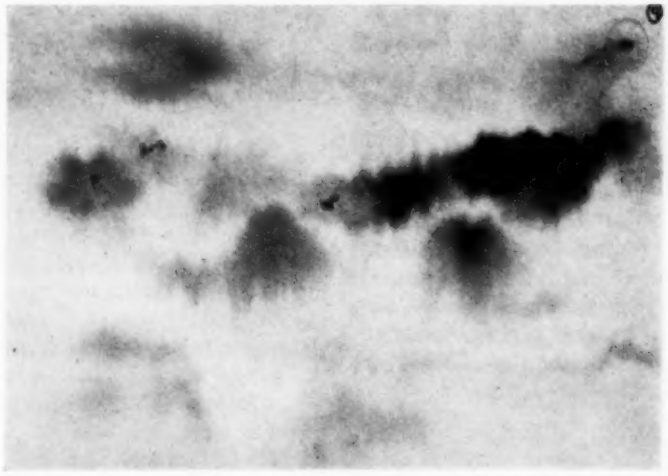


Fig. 13.—A premature infant (No. 2) on the sixty-seventh day. Proline and hydroxyproline are being excreted in much greater amounts than by the full-term infants.

Fig. 14.—A normal full-term infant (No. 77) aged 131 days. Taurine is almost completely absent, β-amino-isobutyric acid is present in high concentration and leucine, valine, and tyrosine are present in slightly larger amounts than normal; otherwise the pattern resembles that of a normal child over 1 year of age.

were healthy. The serum was separated and examined for amino acids as described above.

There was considerable variation from one specimen to another, but certain well-defined differences appeared between the amino acids of these specimens and those of blood from older children. Taurine, lysine, ethanolamine, β-amino-isobutyric acid, tyrosine, and glutamic acid were present in excess of the amounts found in the blood of older children. The amounts of leucine, valine, alanine, and proline were about the same as in older children. One specimen differed from the others in containing only faint traces of amino compounds other than taurine, though this was present in high concentration.

TABLE V. AMINO ACID CONTENT OF CORD BLOOD
(Eleven Specimens)

	MG. PER 100 ML. SERUM			
AMINO-COMPOUND	MIN.	MAX.	MEAN	S. D.
Taurine	2	12	7	3
Ethanolamine	0.0	1.5	0.5	0.3
Lysine	4	20	10	5
Proline	0	10	3	2.9

DISCUSSION

There is a characteristic pattern of amino acid excretion for each age group. On the first day of life almost all infants showed a very similar pattern, which is sometimes seen again on the second or third day, but which changes radically after the fourth day. There is again a change on about the seventh day and further changes continue until the fifth month of life in the full-term infant, and later in the premature infant.

The excretion of amino acids by jaundiced infants did not differ significantly from that of other infants in this series. This was so, whether the jaundice was due to "physiological" jaundice of the newborn infant or to Rh incompatibility.

Hydroxyproline and Proline.—The excretion of these two amino acids show close similarities. In the first few days of life both premature and full-term infants excrete small amounts of hydroxyproline. At about the seventh day, in full-term infants, the amount of hydroxyproline in the urine rises suddenly and remains high till the fifth month, when it drops to very low levels. In premature infants, the steep rise in hydroxyproline excretion occurs at an average age of 4 weeks, and it does not vanish from the urine till after the seventh month in some instances. The excretion of large amounts of hydroxyproline in a chromatogram pattern of the type found in infancy has no parallel among older children or adults, but appears to be characteristic of the first months of life. There is a trace of hydroxyproline in the blood of these infants, but none detectable in the blood of older children or adults.

Proline is absent from the urine of all but the smaller premature infants during the first few days of life. Between the sixth and the ninth day, in full-term infants, proline appears in the urine and its excretion rises rapidly, paralleling the excretion of hydroxyproline in a remarkable manner. Proline vanishes from the urine after about the fifth month. In premature infants the rise and fall in proline excretion again parallels hydroxyproline excretion. Premature and full-term infants from the first day of life, older children, and adults resemble one another in the high concentration of proline in the blood.

In older children the excretion of free proline in detectable amounts is invariably associated with a failure of reabsorption in the renal tubules,[32] except in the massive amino-aciduria of severe hepatic dysfunction. In renal tubular dysfunction of older children the urinary proline is usually, but not invariably, associated with excessive amounts of leucine and valine. Therefore, the large amounts of proline in the urine of infants, in the presence of a normal serum level, can only mean a lower rate of renal tubular reabsorption of proline than in the older child. This is presumably due to immaturity of the kidney. However, this degree of immaturity affects only slightly the reabsorption of the essential amino acids leucine and valine.

The absence of proline from most specimens of urine during the first four days of life can be accounted for by the smaller load of proline presented to the tubule as a result of the diminished glomerular filtration rate at this age.[17, 18] Between the sixth and the ninth days, in full-term infants, the glomerular filtration rate rises, the maximum rate of tubular reabsorption of proline is exceeded, and the excess appears in the urine. The disappearance of proline from the urine after the fifth month presumably reflects the increased ability of the renal tubule to reabsorb proline as the kidney becomes more mature.

The smaller premature infants, but not the larger, excrete a little proline from birth onward, evidence of more marked renal tubular dysfunction. A sharp rise in proline excretion takes place in all the premature infants, on the average, three weeks later than in full-term infants. This equals the average period of prematurity in this series, and probably represents the extra period required for the glomerular filtration rate to rise in the maturing kidney. In premature infants it takes longer than in full-term infants for the renal tubule to acquire the ability to reabsorb all the proline in the glomerular filtrate.

The explanation of the presence of hydroxyproline in the blood must be either a diminished ability as compared with that of older children to catabolize this amino acid, or an increased rate of production from the breakdown of a collagen.[9] Little is known of the normal pathway of hydroxyproline metabolism,[30] although an adult excreted only 15 mg. of free hydroxyproline after ingesting 3.5 Gm., indicating a very rapid metabolism.*

A barely detectable trace of hydroxyproline in the plasma resulted in a marked urinary excretion, both in an adult* and in infants, suggesting that the renal threshold for hydroxyproline is very low. Hydroxyproline excretion follows proline excretion so closely that some common mechanism must be postulated. If both substances were reabsorbed at a common site in the renal tubule, and proline was reabsorbed preferentially to hydroxyproline, then the increase in the glomerular filtration rate would present the tubule with more proline than could be reabsorbed, and this would

*_Hydroxyproline feeding experiment_: A normal adult weighing 70 kilograms ingested 3.5 Gm. of L-hydroxyproline in about 250 ml. of water. Thirty minutes later his blood contained about 500 μg of hydroxyproline per 100 ml. plasma, (i.e., at the level just detectable with certainty); the plasma levels of proline and other amino acids were normal. The urine passed during the first hour after taking the hydroxyproline contained 25 μg in the standard volume; all other amino acids were normal and proline was absent. In all, 15 mg. of hydroxyproline was excreted, all within the first two hours.

block the reabsorption of hydroxyproline. Hence, both proline and hydroxyproline would appear in the urine in comparable amounts.

In young infants, the renal tubule is presented with far more hydroxyproline in the glomerular filtrate than in older children. This might suggest that the hydroxyproline blocks the reabsorption of proline, and thus causes the excretion of proline and hydroxyproline simultaneously. This is the converse of the above hypothesis and can be rejected on the following evidence. Proline was absent from the urine, but not the blood, of an adult who excreted an amount of hydroxyproline comparable to these infants after ingesting a test dose. Furthermore, an infant aged 7 weeks, not included in this series, who was fed the bulk of her nitrogen in the form of a casein hydrolysate free from hydroxyproline, excreted normal amounts of proline for her age, but no hydroxyproline. Before this special diet was instituted she was breast fed, and both proline and hydroxyproline were present in the urine.[35]

These results show that hydroxyproline in the glomerular filtrate does not hinder the reabsorption of proline in the adult kidney and that an infant can excrete proline in the absence of hydroxyproline.

Taurine, Cystine, and Lysine.—Taurine is present in large amounts in the urine passed a few seconds after birth, and must, therefore, be excreted by the fetal kidney. The average amount excreted falls to a low value in the course of the first four days of life. It then rises from about the tenth to the fiftieth day in both premature and full-term infants. In many specimens, however, taurine is absent from the urine, a finding never encountered among children over 1 year of age on a normal diet.

Most specimens of urine high in cystine were low in taurine. There is also a marked positive correlation between the amount of cystine and the amount of lysine present in a specimen of urine, and a negative correlation between the amounts of lysine and taurine.

The large amounts of taurine present in cord blood, fetal urine, and the urine of the first days of life can best be explained by some peculiarity of fetal metabolism. There are three possibilities: the placenta may concentrate taurine as it does certan α-amino-acids[4] but, unlike these, taurine has no known function. Alternatively, the mechanism for taurine catabolism may not be fully formed. As the third possibility, more taurine may be formed than in the older child, because alternative pathways for cystine metabolism are not functioning efficiently.

The moderate rise in taurine excretion occurring about the tenth day is probably due to the increase in glomerular filtration rate that occurs then combined with a low rate of renal tubular reabsorption. The higher excretion of taurine in premature infants than in full-term infants from the fifteenth to the fiftieth day of life is probably due to the latter factor. The very low taurine levels (5 μg or less) in some specimens of urine during the first two weeks of life seemed to be associated with a high cystine output. This can possibly be explained by a reduced production of taurine from cystine, following the loss of excessive amounts of cystine in the urine, as it is known that taurine

is an intermediate metabolite of cystine, some cystine being converted to taurine, and some cystine to inorganic sulfate. On the other hand the fall in urinary taurine levels that occurs about the fiftieth day may be due to a change from human to cow's milk feeds. Jonxis[13] found that infants fed cow's milk excreted less taurine than infants fed human milk; cow's milk contains much less cystine than human milk.

The plasma lysine level was high both in cord blood and on the first day of life. Subsequently it fell but remained higher than in older children. This suggests a reduced rate of catabolism of lysine for a time after birth, since lysine cannot be synthesized by the body. In the fetus this may be accompanied by a placental concentration gradient for lysine.

The variability of urinary lysine excretion from infant to infant, in the absence of corresponding changes in blood level, reflects the variation in the efficiency of renal tubular reabsorption of lysine. On the other hand, the relative constancy of lysine excretion in different specimens from the same infant suggests that a true difference in renal maturity is involved. The reabsorption of the bulk of the lysine in the glomerular filtrate in some infants, in spite of the raised blood level, may signify greater functional maturity of the kidney. Excretion of lysine in amounts greater than 7 μg in the calculated volume suggests renal tubular immaturity; such an excretion of lysine is commoner among premature than full-term infants. The association of lysine with cystine supports previous evidence that lysine and cystine are reabsorbed at a common site in the renal tubule.[10] The much smaller proportion of older children and adults than of infants excreting large amounts of lysine and cystine suggests that, in the majority of cases, the renal tubule acquires the ability to reabsorb lysine and cystine during the first year of life.

Ethanolamine.—A high rate of production or a low rate of catabolism of ethanolamine in the fetus and newborn infant is suggested by its presence in their blood, since ethanolamine is not found in the blood of older children or adults.

The high excretion of ethanolamine in utero and on the first day of life in full-term infants can be contrasted with its excretion in premature infants, where the peak is not reached till the sixth day. In both full-term and premature infants there is thereafter a steady decrease in ethanolamine excretion with time, the two curves running roughly parallel and, on the average, with a three-week interval on the abscissa.

In older children excretion of notable amounts of ethanolamine occurs in liver disease,[32] and it is possible that its excretion in the newborn infant is associated with hepatic immaturity.

β-Amino-Isobutyric Acid.—There is considerable variability in the excretion of this β-amino-acid in all age groups. The average amount excreted by neonates is, however, considerably higher than the average amount excreted by older children and may be explained by the high blood level in neonates. In the fetus the blood and urinary levels are still higher. This in turn suggests a metabolic difference, but very little is known about the

metabolism of this β-amino-acid except that it can apparently be derived from nucleic acid.[7]

Tyrosine.—There is a marked positive correlation between the amount of tyrosine excreted and the degree of prematurity. This might be due to a renal tubular leak or to the reduced ability of premature infants to metabolize tyrosine,[14, 34] but as the blood was not examined in these particular cases, nor the urine investigated for intermediate metabolites of tyrosine, it is not possible to decide between these alternatives.

Conjugated Amino Acids.—The close similarity between the urinary conjugated amino acids of adults and of infants less than 4 days old, as found in this series, is in striking contrast to the differences in free amino acids. This similarity extends to the different fractions as well as to the total amount of conjugated amino acids.

The identity of the conjugated amino acids adsorbed by the acid resin, Zeo-Karb 225, is not known. Since, however, the resin used will adsorb only small basic molecules, they probably are mostly di- , tri- , and tetrapeptides.

In both adults' and infants' urine the fraction adsorbed by the weak-base resin consists largely of conjugates of glycine and glutamic acid. In adults it has been shown that hippuric acid and phenylacetylglutamine are the more important components of this fraction.[29] If this is true of infants, it suggests that the ability to produce benzoic and phenylacetic acids, and to conjugate (i.e., "detoxicate") them, is well developed by the second day of life.

The conjugated amino acids adsorbed by neither resin may be combined as polypeptides, proteins, or mucoproteins with too high a molecular weight to be adsorbed, or as cyclic peptides with no free amino or carboxyl groups, or conjugated with sugars or sugarlike substances.

Sugars.—Lactose was, of course, present in all feedings and, from about the sixth day, sucrose was present in some of the artificial feedings. The absence of large amounts of these sugars from the urine in most cases, with the presence of galactose and sometimes fructose, is evidence of the normal activity of lactase and sucrase in the gut, assuming normal absorption; lactase appeared to be active even in a 32-week premature infant (No. 4) on the fourth day of life.[11] An exception was the infant who, at the age of 3 days, was given feedings containing sucrose and who excreted large amounts of sucrose in the urine, but no fructose; his galactose, lactose, and glucose excretions were normal. This may be taken to indicate normal lactase and diminished sucrase activity.

Fructose and galactose were generally present in the urine in only moderate amounts, indicating efficient conversion to glucose and glycogen in the liver. An exception to this was the presence of large amounts of fructose in the urine of one very premature infant, who was being fed fairly large amounts of sucrose, indicating a saturation of the capacity of the liver to deal with fructose, possibly on account of immaturity.

Glucose was occasionally present in amounts up to 20 mg. per 100 ml. of urine in infants in this series, while in normal older children values above 5

mg. per 100 ml. are rare. Norval and associates[20] found that the blood sugar level in infants during the first six days of life was 61 ± 15.6 mg. per 100 ml. (mean ± standard deviation), while later the blood sugar rose to the adult level.[25]

The presence of glucose in the urine while the blood sugar level is so low suggests that there is reduced renal tubular ability to reabsorb glucose. This would fit in with the evidence of renal immaturity suggested by the pattern of amino acid excretion, but the fact that only a small amount of glucose was excreted suggests that, in respect to glucose, over-all renal tubular function at this age is nearly as efficient as in the older child. Possibly a few nephrons have a markedly lowered threshold for glucose, while the majority have thresholds above the blood glucose level.

Concentration.—As measured by creatinine concentration, the fetal urine is very dilute indeed, but within a few hours of birth the full-term infant's urine has become very concentrated, the concentration then falling steadily during the next few days of life. This may be interpreted as a rapid assumption by the renal tubule of the power of reabsorbing water, perhaps its most important function, followed by the passing of more dilute urine as the intake of fluid increased. Only very few infants excreted a concentrated specimen of urine after the fourth day of life. Some of these were dehydrated, but it was not true of all of them and some apparently dehydrated infants passed dilute specimens of urine.

Premature infants did not concentrate their urine, during the first three days of life, to the same extent as full-term infants, again suggesting that their kidneys are less mature in function. The slight rise in concentration on the third and fourth days may have been due to dehydration.

CONCLUSIONS

We suggest that the various changes in excretion of amino compounds in infancy are determined by alterations in the metabolism in the developing infant and by the functional maturity of the renal tubules and glomeruli.

Our findings lead us to believe that:

1. The presence of proline in the urine is due to a low rate of renal tubular reabsorption.

2. During the first few days of life in full-term infants, and first weeks of life in most premature infants, the low glomerular filtration rate masks this tubular inefficiency and causes proline to be absent from the urine.

3. In the smallest premature infants the renal tubule is relatively even less efficient and permits the excretion of proline during the first few days.

4. The excretion of large amounts of lysine and cystine by a proportion of infants is the result of a similar dysfunction of the renal tubules.

5. On the other hand, in all but the smallest premature infants, the renal tubules can reabsorb glucose and the essential amino acids leucine and valine nearly as efficiently as in the older child.

The increased concentrations of taurine, lysine, ethanolamine and β-amino-isobutyric acid in the blood and urine of the fetus are probably due to differences in metabolism. These differences may be due to placental action or "immaturity" of the liver. The delay in fall of urinary ethanolamine and β-amino-isobutyric acid,

and the persistent high blood lysine level after birth may indicate that the liver is primarily responsible in respect to these amino compounds.

SUMMARY

The amino acids have been examined in 273 specimens of urine from 119 infants, aged from a few hours to 8 months. Sixty of these specimens have been examined for sugars. In addition, six specimens of fetal urine have been examined for amino acids and sugars. The amino acids have been examined in twenty-four specimens of venous or capillary blood from these infants, and twelve specimens of blood from the umbilical cord.

The plasma contained far more lysine, ethanolamine, β-amino-isobutyric acid and, in the case of cord blood, taurine than did that of older children. These amino compounds were also present in high concentration in urine passed at birth. The amounts excreted fell progressively thereafter but at different rates for the different amino compounds.

From about the sixth day in full-term infants, or the fourth week in premature infants, the urine contained high concentrations of proline and hydroxyproline, dropping to the very low levels normal for older children by the fifth to the seventh month.

About a third of the specimens of urine, particularly those from premature infants, contained more lysine and, often, more cystine than those from older children.

Glucose was present in about one-third of the specimens in concentrations slightly exceeding those found in older children. Fetal urine contained small amounts of fructose and glucose and, in one case, a sugar tentatively identified as mannose.

The appearance in blood and urine of greater amounts of taurine, lysine, ethanolamine, β-amino-isobutyric acid and hydroxyproline than in the older child is considered to be due to quantitative or qualitative differences in the intermediary metabolism of these compounds.

A less efficient renal tubular reabsorption mechanism than in the older child is probably responsible for the increased excretion of proline and, in some cases, lysine and cystine; this lower efficiency is more marked and lasts longer in the premature than in the full-term infant.

A low glomerular filtration rate during the first few days of life in the full-term infant, or first few weeks of life in the premature infant, is considered responsible for the relative absence of proline and hydroxyproline from the urine during this period.

We wish to thank the nursing staff of Queen Charlotte's Maternity Hospital for collecting the majority of specimens. Acknowledgments are also due Dr. H. V. L. Finlay of Hillingdon Hospital and the staff of the Premature Baby Unit at Hammersmith Hospital for their help. Our thanks are due Mr. Peter Cull and Mr. G. V. G. Lythe, of the Department of Medical Illustration at The Hospital for Sick Children, who drew Figs. 1 to 8.

The laboratory investigations were made possible by the Research Committee of The Hospital for Sick Children, which allowed one of us (L. I. W.) a research fellowship.

REFERENCES

1. Barlow, A., and McCance, R. A.: Arch. Dis. Childhood **23**: 225, 1948.
2. Bickel, H.: Ph.D. Thesis, University of Birmingham, 1952.
2a. Black, J. A.: Arch. Dis. Childhood **26**: 618, 1951.
3. Childs, G.: Proc. Soc. Exper. Biol. & Med. **81**: 225, 1952.
4. Christensen, H. N., and Streicher, J. A.: J. Biol. Chem. **175**: 95, 1948.

5. Consden, R., Gordon, A. H., and Martin, A. J. P.: Biochem. J. **38**: 224, 1944; Biochem. J. **41**: 590, 1947.
6. Dustin, J. P., Moore, S., and Bigwood, E. J.: Metabolism **4**: 75, 1955.
7. Fink, R. M., Fink, K., and Henderson, R. B.: J. Biol. Chem. **201**: 349, 1953.
8. Goebel, F.: Ztschr. Kinderh. **34**: 94, 1922-1923.
9. Harkness, R. D., Marko, A. M., Muir, H. M., and Neuberger, A.: Biochem. J. **56**: 558, 1954.
10. Harris, H., Mittwoch, U., Robson, E. B., and Warren, F. L.: Ann. Human Genetics **19**: 196, 1955.
11. Ibrahim, J.: Ztschr. f. physiol. Chem. **66**: 19, 1910.
12. Jonxis, J. H. P.: Arch. Dis. Childhood **26**: 272, 1951.
13. Jonxis, J. H. P.: Voeding **12**: 309, 1951.
14. Levine, S. Z., Marples, E., and Gordon, H. H.: J. Clin. Invest. **20**: 199, 1941.
15. Lo Bianco, S.: Boll. Soc. It. Biol. sper. **29**: 1134, 1953.
16. Lo Bianco, S.: Lattante **24**: 781, 1953.
17. McCance, R. A., Naylor, N. J. B., and Widdowson, E. B.: Arch. Dis. Childhood **29**: 104, 1954.
18. McCance, R. A., and Widdowson, E. M.: Arch. Dis. Childhood **29**: 488, 1954.
19. Morton, P. M., Pratt, E. L., and Hasselman, E.: Abstracts of 24th annual meeting of Society for Pediatric Research, p. 15, 1954.
20. Norval, M., Kennedy, R. L., and Berkson, J.: J. PEDIAT. **34**: 342, 1949.
21. Peters, J. P., and van Slyke, D. D.: Quantitative Clinical Chemistry; Interpretation, vol. 1, pp. 898, 908, 1946.
22. Schreier, K., and Plückthun, H.: Biochem. Ztschr. **320**: 447, 1950.
23. Sereni, F., McNamara, H., Shibuya, M., Kretchmer, N., and Barnett, H. L.: Pediatrics **15**: 575, 1955.
24. Simon, S.: Ztschr. Kinderh. **2**: 1, 1911.
25. Smith, C. A.: The Physiology of the Newborn Infant, ed. 2, Oxford, Blackwell Scientific Publications, Ltd., 1951.
26. Souchon, F.: Ztschr. ges. exper. Med. **118**: 219, 1952.
27. Souchon, F., and Grunau, G.: Ztschr. ges. exper. Med. **119**: 641, 1952.
28. Souchon, F., and Grunau, G.: Arch. Kinderh. **114**: 143, 1952.
29. Stein, W. H., Paladini, A. C., Hirs, C. H., and Moore, S.: J. Am. Chem. Soc. **76**: 2848, 1954.
30. Stetten, M. R.: A Symposium on Amino Acid Metabolism, McElroy, W. D., and Glass, H. B., eds., Baltimore, 1955, Johns Hopkins Press, p. 277.
31. Stroder, J., Grunhofer, H., and Heim, L.: Ann. paediat. **180**: 52, 1953.
32. Woolf, L. I.: Great Ormond Street J. **1**: 61, 1951.
33. Woolf, L. I.: Nature **171**: 841, 1953.
34. Woolf, L. I., and Edmunds, M. E.: Biochem. J. **47**: 630, 1950.
35. Woolf, L. I.: Unpublished data.

LOEFFLER'S PNEUMONIA ASSOCIATED WITH HYPOGAMMAGLOBULINEMIA

CHARLES AZIZA, M.D., AND JOSEPH H. LAPIN, M.D.
NEW YORK, N. Y.

RECENT work on the relationship of low levels of blood gamma globulin to susceptibility to infection[1, 2, 3] stimulated us to report this case of Loeffler's transitory, migratory pneumonia associated with eosinophilia, which showed clinical benefit from injections of gamma globulin.

CASE REPORT

The patient, R. M., aged 3½ years, hospital No. 278014, had been adopted at 10 days of age, so that no family history is available. He did well until 7 months of age, when he developed an upper respiratory infection associated with wheezing. After three weeks, he became severely dyspneic, with infracostal retraction but with no hoarseness or cyanosis. Physical examination on admission showed acute respiratory distress with prolonged expiration, moderate infracostal retraction, and inspiratory and expiratory wheezing on the left side; there was no cyanosis or voice changes and no fever at this time; pulse was 130, and respiratory rate 50 per minute.

X-ray of the chest showed consolidation of the left lower lobe with an initial white blood cell count of 24,000 with 79 per cent segmented forms. Tuberculin tests and blood cultures were negative. On oxygen, with penicillin and Terramycin intramuscularly, the temperature rose to 103° F. and the child became severly dyspneic, restless, and cyanotic, with blood-tinged, frothy expectoration. Improvement became evident by the second day and x-rays on the fourth and seventh days were negative. Because of an episode of diarrhea, cystic fibrosis was considered, but the stools were negative for starch and fat, and trypsin was present in 1:100 dilution. The blood count on the fourteenth day had fallen to 10,000, with 35 per cent segmented forms and 9 per cent eosinophils. The child was discharged after two weeks in the hospital.

The essential facts of his other hospital admissions are shown in Table I. During his second hospital stay, of eighteen days, three separate pulmonary infiltrations were discovered, one accompanied by clinical signs of pneumonia, leukocytosis and polynucleosis, and the other two by eosinophilia only. Another pneumonic episode resulted in a third admission for eighteen days, during which bronchoscopy was done to rule out a foreign body. During the next nine months at home, in which he was treated with 25 to 50 mg. of cortisone three times a day, he seemed under control except for a few upper respiratory infections accompanied by wheezing which seemed to increase when he ate strawberries, green peas, beets, and sweet potatoes. He had only slight reactions on intradermal testing with inhalants, molds, and most of the common foods. The fourth admission, of ten days, was made necessary by severe status asthmaticus, with little relief from any medication. The final, fifth admission, of four months in the hospital, is summarized in Table I and shows four separate episodes of pulmonary infil-

From Pediatric Service of the Bronx Hospital.

trations, usually associated with clinical symptoms, fever, and leukocytosis, and during the last seven weeks in the hospital, continuous treatment with erythromycin and ACTH or cortisone was instituted and he was given gamma globulin in doses ranging from 5 c.c. each week to 15 c.c. every two weeks. To this point, no further pneumonias have been reported.

During the last admission, trypsin was again found in the stools but no starch or fat, and the concentration of chlorides in the sweat was 42 meq. per liter, normal for our technique. A bronchogram was negative. The blood total protein was 6.5 grams per cent, albumin 4.6, and globulin 1.9 grams per cent. The gamma globulin level by the Tiselius method was 5.43 per cent. The child's blood group is A; the anti-B titer was 1:64. No Schick test could be done as injections had not been completed.

For the last eighteen months he has been at home on 200 mg. of erythromycin a day, 37.5 mg. cortisone daily, and 10 c.c. of gamma globulin every two weeks. Monthly x-rays of the chest have been negative and the blood eosinophils have never exceeded 2 per cent. He tolerates all the foods and has been well except for slight wheezing when cortisone is omitted.

The gamma globulin level rose to 6.22 per cent at 2½ years of age and 10.40 per cent at 3 years 3 months, and the child is now getting Meticorten, 5 mg. daily, and gamma globulin, 10 c.c. monthly.

DISCUSSION

A summary shows that our patient experienced at least nine episodes of pneumonias, roentgenologically proved, in the period from 7 months to 2 years of age, as well as one episode of severe status asthmaticus. Since injections of gamma globulin have been added to the regime of antibiotics and cortisone he has been free of pneumonia for the eighteen months to date.

In this age group in the New York area, the pulmonary manifestations of cystic fibrosis of the pancreas are statistically the most common cause of such frequent pulmonary infections,[4] but this diagnosis was adequately excluded by the absence of steatorrhea, the normal trypsin in the stools, and the normal chlorides in the sweat. Bronchiectasis has been excluded by the normal bronchogram. A foreign body was unsuccessfully sought for by bronchoscopy. Pulmonary manifestations of helminthiasis were disproved by repeated negative examinations of the stools for ova and parasites. The clinical course and the repeatedly negative tuberculin tests ruled out pulmonary tuberculosis. Familial dysautonomia was deemed improbable because of the presence of tears and the absence of any automonic nervous system symptoms.

The question then left to be solved was whether this was an allergic child who had nine episodes of bacterial pneumonia, fortuitously, or one who had Loeffler's transitory migratory pneumonias or one in whom hypogammaglobulinemia was responsible for nine attacks of bacterial pneumonias. While intradermal tests were positive only to house dust and a few foods and clinical observation did not confirm the etiological importance of these skin reactions, nevertheless the episode of an afebrile status asthmaticus, the eosinophils both in the nasal smear and in the sputum, and the almost invariable blood eosinophilia make the diagnosis of underlying allergic pulmonary disease almost certain.

In Loeffler's syndrome, multiple etiologies have been considered[5]: allergy, parasitic infestation, tuberculosis, and

TABLE I. CLINICAL COURSE PRIOR TO THE GAMMA GLOBULIN TREATMENT

DATES	AGE	CLINICAL COURSE	WBC	POLYS. (PER CENT)	EOSIN. (PER CENT)	SKIN TESTS	SPUTUM	NOSE AND THROAT	STOOLS
11/23/53 (First admission)	7½ mo.	Pneumonia left lower lobe; 103° F.	24,000	79		Tuberculin tests negative			Trypsin: 1:100+; starch and fat: negative
12/ 8/53		Improved	11,000	35	9				
12/10/53 (Second admission)		Pneumonia left upper lobe; 102° F.	22,000	77		House dust: 1:100 slight 1:10 moderate		Nose smear: moderate eosinophils	
								Culture: aerogenes; subtilis; nonhemolytic *Str. faecalis*	Negative for ova and parasites
12/24/53		Pneumonia right upper lobe; asymptomatic	12,000	29	13				
12/28/53		Pneumonia right lower lobe; asymptomatic	10,000	35	9				
1/ 5/54 (Third admission)		Pneumonia left mid-lung; 101° F.	6,000	84			Smear: numerous eosinophils; culture: alpha hemolytic streptococcus and *Esch. coli*		Trypsin: 1:200+

1/ 6/54		Relatively well for 9 mo.	12,000	26	15				
10/13/54 (Fourth admission)	20 mo.	Status asthmaticus: 102° F.; no pulmonary infiltrations	14,000	70		Tuberculin test negative			
10/21/54			11,000	32	8				
10/25/54 (Fifth admission)		Pneumonia left lower lobe; afebrile	13,000	46	5		Culture: nonhemolytic *Str. faecalis* and *A. aerogenes*	Nose smear: many eosinophils Throat culture: hemolytic *Str. faecalis* and *Esch. coli*	Negative for ova and parasites
11/ 2/54					9				
11/ 8/54					10				
11/20/54		Patchy densities in both bases; 103° F.	6,000	74					
11/26/54			8,600	28	13				
12/18/54		Pneumonia left base, 102° F.	11,000	38	4				
1/ 7/55		Pneumonia right mid-lung	4,500	64	2				
2/21/55	2 yr.		12,500	58	4				

bacterial infections. In those due to helminthiasis, the high eosinophil count is concomitant with the lung infiltration, whereas in cases similar to our own[6] eosinphilia did not appear until the third or fourth episode of pneumonia. The peak of eosinophilia is supposed to occur after the appearance of the pulmonary infiltration[7] and in cases[8] with a stormy course (episodes of cyanosis and apnea) the eosinophilia appeared only on the eighth day, increasing to 41 per cent by the eleventh day. In one case,[9] a white blood cell count of 325,000 with 72 per cent eosinophils necessitated bone marrow studies to rule out the possibility of eosinophilic leukemia. While Loeffler's syndrome has been reported to occur mainly in July and August, in our case the repeated episodes of fleeting pneumonias appeared in two consecutive winters. Harkavy[10] reported pulmonary infiltrations with eosinophilia lasting many years in patients with asthma of bacterial origin. The roentgenologic findings have been reported similar to those in pertussis and epituberculosis[11] or to the exudative type of tuberculosis.[12] In fact, Loeffler did tuberculin tests on all his patients and found that one later developed tuberculosis.

In favor of the allergic etiology of the transient pulmonary infiltrations is Blanton's[13] finding that injections of epinephrine resulted in a transient complete clearing of the infiltrations, which returned the following day. Clinical improvement has been claimed from the injections of ACTH; de Vries and co-workers[14] noticed a leukocytosis associated with eosinopenia and lymphopenia, but this lasts only twenty-four hours, with the lymphocytes increasing above their initial levels.

In our patient, the leukocytosis was observed before any treatment with ACTH or cortisone, which is confirmed by the cases reported by Squier[6] and Karan and Singer.[12] Since eosinophilia is by no means an uncommon accompaniment of infections, both in premature babies and in early infancy, the etiological significance of Loeffler's syndrome of transient pulmonary infiltrations associated with eosinophilia has always been doubted by critical workers. We can find no reference in the literature to gamma globulin estimations in any group of such patients. It, therefore, seems possible that many of the so-called Loeffler's syndrome cases were really repeated bacterial pneumonias due to agammaglobulinemia or hypogammaglobulinemia.

The gamma globulin level slowly rises from infancy to adult life, but the spread of values is so wide that great caution must be taken in judging any particular figure. Thus Knapp and Routh,[15] in a study of gamma globulin levels in normal children free of infection for at least one month, gave the range from 18 months to 4 years of age as 3.3 to 12.1 per cent, with a mean value of 7.2 per cent. Corbeil and associates[16] report a mean level of 8.3 per cent between 1 and 2 years of age by the Tiselius method. Hayles and colleagues[17] consider 12.1 per cent as the normal value in this age group and Orlandini and co-workers[18] gave 8.54 ± 1.13 per cent for 12 to 18 months, and 10.15 ± 1.78 per cent for 18 to 24 months. By our standards, employing the Tiselius electrophoretic method, the normal values from 1 to 3 years of age are 8.8 ± 1.2

per cent. We may, therefore, assume that our patient's value of 5.43 per cent, rising to 6.2 and finally to 10.40 per cent after months of injections, is somewhat low.

In general there are three different syndromes associated with gamma globulin deficiency. First are the groups reported by Janeway and associates[19] with hypergammaglobulinemia and repeated nonspecific infections, in which the infection may start in the neonatal period and in which the tendency to infection can be lessened by injections or normal gamma globulin. This "dysgammaglobulinemia" may be similar the the group reported earlier by Zuelzer and Apt[20] in which transient pulmonary infiltrations, marked leukocytosis, eosinophilia up to 80 per cent, and hepatomegaly were associated with hyperproteinemia due to an increase in the gamma globulin fraction up to 38 per cent.

Second is the group in which hypoproteinemia and hypogammaglobulinemia are associated with edema.[21-23] Repeated infections may be absent, for which fact the explanation given is that antibodies may be present in the other globulin fractions and also in the tissues. One such case has been reported associated with eosinophilia.[23]

Third, only the gamma globulin fraction is decreased, together with a tendency to frequent infections. The syndrome has been reported congenital,[1, 2] or acquired.[24-26] However, our case seems to be the first reported in the literature in which an initially low level rises during the period of injections to almost double the previous level. Whether this means that the very high doses of gamma globulin injected raised the level of gamma globulin or that there was a concomitant increase in the ability of the body to manufacture gamma globulin cannot be answered now.

The role which gamma globulins play in immunity is obviously difficult to describe. We know there are specific gamma globulins, those without any immunologic activity; we know that some antibodies migrate with alpha globulin and beta globulin[27] and we know the role of properdin. Even the nature of the primary deficiency in gamma globulin is not sure; it seems to be a morphologic failure of plasma cell differentiation in the lymph nodes[28] as well as a decrease of plasma cells in the bone marrow.[29] The ability of these agammaglobulinemic children to develop a nonspecific tolerance to infection, mainly to the gram-negative group of organisms, seems to stem from "an acute phase reaction," but so far as is known they do not develop any true antibodies. Other modes of reaction have been reported,[29] for example, the marked eosinophilia in staphylococcic infection. They respond to ACTH by an eosinopenia, proving the integrity of the pituitary-adrenal system.

While agammaglobulinemia is a chronic disease, hypogammaglobulinemia may be transitory.[30] One form is the transitory stage in the newborn infant, occurring between the second and the third month, perhaps also in those premature infants with low levels. Another is the idiopathic hypogammaglobulinemia developed during severe bacterial infections, which returns to a normal level after recovery. In a group of twenty-five patients presenting infections refactory to antibiotics, Schick and Harris[31] reported recovery following a few injections of gamma globulin (0.6 to 0.8 c.c. per

Kg.); unfortunately no figures of gamma globulin levels were given in these cases.

No definitive critical judgment on the etiological relationship of hypogammaglobulinemia to infection is as yet possible. The recent review by Good and Zak[32] mentions as one group of patients "children having transient hypogammaglobulinema of infancy associated with an apparent delay in assumption of immunologic responsibility." Our case seems to fall into this group.

SUMMARY

A case has been presented of a child who developed nine episodes of pneumonia associated with eosinophilia between 7 months and 2 years of age. Since then, with large doses of gamma globulin, he has had no febrile infection and his gamma globulin level has practically doubled from its initial low level of 5.43 per cent. The literature of Loeffler's syndrome and on agammaglobulinemia and hypogammaglobulinemia has been reviewed.

We wish to thank Dr. H. Boynton of the American Red Cross (New York) for the generous supply of gamma globulin.

REFERENCES

1. Bruton, O. C.: Agammaglobulinemia, Pediatrics **9**: 722, 1952.
2. Bruton, O. C., Apt, L., Gitlin, D., and Janeway, C. A.: Absence of Serum Gamma Globulins, A. M. A. Am. J. Dis. Child. **84**: 632, 1952.
3. Gitlin, D.: Low Resistance to Infection: Relationship to Abnormalities in Gamma Globulin, Bull. New York Acad. Med. **31**: 359, 1955.
4. Di Sant'Agnese, P.: Bronchial Obstruction With Lobar Atelectasis and Emphysema in Cystic Fibrosis of the Pancreas, Pediatrics **12**: 178, 1953.
5. Nemir, R. L., Heyman, A., Gordon, J. D., and Nervin, E.: Pulmonary Infiltrations and Eosinophilia in Children (Loeffler's Syndrome), J. PEDIAT. **37**: 819, 1950.
6. Squier, T. L.: Transitory Pulmonary Infiltrations, Dis. Chest **13**: 609, 1947.
7. Scheer, E. H.: Loeffler's Syndrome, Arch. Pediat. **68**: 407, 1951.
8. Ham, J. C., and Zindall, W. T.: Loeffler's Syndrome and Pulmonary Infiltrations Accompanied by Peripheral Eosinophilia, Ann. Int. Med. **29**: 488, 1948.
9. Grimmet, M. H., Williams, J. O., and Williams, M. L.: Loeffler's Syndrome, North Carolina M. J. **13**: 337, 1952.
10. Harkavy, J.: Vascular Allergy, J. Allergy **14**: 507, 1943.
11. Pujol, Alfredo, Jr.: Loeffler's Syndrome, Ann. paulist. med. e cir. **52**: 321, 1946.
12. Karan, A. A., and Singer, E.: Transitory Pulmonary Infiltrations Mistaken for Tuberculosis With a Report of Five Cases, Ann. Int. Med. **17**: 106, 1942.
13. Blanton, H. W.: Observations on Loeffler's Syndrome, Report of Four Cases, Virginia M. Month. **72**: 473, 1945.
14. De Vries, J. A., Herbert, P., and Rose, B.: Studies on the Effect of ACTH on Loeffler's Syndrome and Tropical Eosinophilia, J. Allergy **21**: 12, 1950.
15. Knapp, E. L., and Routh, J. I.: Electrophoretic Studies of Plasma Proteins in Normal Children, Pediatrics **4**: 508, 1949.
16. Corbeil, L., Lahey, E., and Guest, G. M.: L'Hypogammaglobulinemie chez l'enfant, Arch. franç. pediat. **11**: 562, 1954.
17. Hayles, A. B., Sticker, G. B., and McKenzie, F.: Decrease in Serum Gamma Globulin, Report of Three Cases, Pediatrics **14**: 450, 1964.
18. Orlandini, O. T., Sass-Kortsak, A., and Ebbs, J. H.: Serum Gamma Globulin Levels in Normal Infants, Pediatrics **16**: 575, 1955.
19. Janeway, C. A., Craig, J. M., Davidson, M., Downey, W., Sullivan, J. C.: Hypergammaglobulinemia Associated With Severe Recurrent and Chronic Nonspecific Infections, A. M. A. Am. J. Dis. Child. **88**: 389, 1954.
20. Zuelzer, W. W., and Apt, L.: Disseminated Visceral Lesions Associated With Extreme Eosinophilia, Am. J. Dis Child. **78**: 153, 1949.
21. Schick, B., and Greenbaum, J.: Edema With Hypoproteinemia, J. PEDIAT. **27**: 241, 1945.
22. Fried, C. T., and Henley, W. L.: Deficiency in Gamma Globulin With Edema and Hypoproteinemia, Pediatrics **14**: 59, 1954.
23. Wyngaardeen, J. B., Crawford, J. D., Chamberlin, H. R., and Lever, W. F.: Idiopathic Hypoproteinemia: Transient Edema, Depression of Plasma Albumin and Gamma Globulin and Eosinophilia, Pediatrics **9**: 729, 1952.
24. Wall, L. R., and Saslaw, S.: Adult Agammaglobulinemia, A. M. A. Arch. Int. Med. **95**: 33, 1955.
25. Seltzer, G., Baron, S., and Toporek, M.: Idiopathic Hypogammaglobulinemia and

Agammaglobulinemia, New England J. Med. 252: 252, 1955.
26. Collins, H. D., and Dudley, H. R.: Agammaglobulinemia and Bronchiectasis. A Report of Two Cases in Adults (Females) With Autopsy Findings, New England J. Med. 252: 255, 1955.
27. Royer, P., Corbeil, L.: Les modifications de la gammaglobulinemie et leur interet en Pediatrie, Semaine hôp. Paris 32: 622, 1956.
28. Craig, J. M., Gitlin, D., Jewett, T. C.: The Response of Lymph Nodes of Normal and Congenitally Agammaglobulinemic Children to Antigenic Stimulation, A. M. A. Am. J. Dis. Child. 88: 626, 1954.
29. Good, R., and Varco, R. L.: Clinical and Experimental Study of Agammaglobulinemia, Journal-Lancet 75: 245, 1955.
30. Janeway, C. A. (quoted by Royer, P., and Corbeil, C.): Seminar on Gammaglobulines, Centre international de l'enfance, Vol. 1, Paris, 1955, Masson et Cie., p. 201.
31. Schick, B., and Harris, J. R.: Gamma Globulin in Infection Refractory to Antibiotics, J. Mt. Sinai Hosp. 31: 148, 1954.
32. Good, R. A., and Zak, S. J.: Disturbances in Gamma Globulin Synthesis as "Experiments of Nature," Pediatrics 18: 109, 1956.

Robert Whytt on Tuberculous Meningitis, 1768

I have already observed, that in the first stage it is hard to discover this internal *hydrocephalus.* But when we meet with a patient under fifteen or sixteen years of age, seized with a slow fever of no certain type, and irregular in its accessions and remissions; when in that fever the patients vomit once a day, or once in two or three days; when they shun the light, and complain of a pain in the crown of their head, or over their eyes, after the fever has continued for some time, or of a achs, (as they are commonly called); but it is observable, that in such cases this kind of pulse is always attended with a cool skin.

When therefore, with a slow and irregular pulse we meet with thirst and a feverish heat, watching, a *strabismus,* or double sight, a *delirium,* and screaming, succeeding the symptoms mentioned in the first stage, we may strongly suspect water in the ventricles of the brain. But this is still more evident, when soon after the patient grows comatose, the pupil dilates and loses its motion, the pulse becomes quick, the cheeks are flushed, the tendons start, and convulsions follow.

It is true indeed, that some of these very symptoms are observed towards the end of common fevers, in which, from the brain being much affected, the patient falls into a *coma* before his death. But a fever from water in the brain is easily distinguished from others, by attending to the whole course of the disease, and particularly to the pulse, which, after having been at first quick, becomes slow and irregular; and lastly acquires a greater frequency than ever. Besides, the screaming, squinting, and dilation of the pupil, rarely occur in other fevers.

PEDIATRIC USE OF DIOCTYL SODIUM SULFOSUCCINATE

FETHI TEVETOGLU, M.D.
CORPUS CHRISTI, TEXAS

CONSTIPATION is a common condition during infancy and childhood.[1] Unfortunately it is usually brought to the physician's attention only if severe or when it has persisted for some time. In many cases there is a history of the use of cathartics, strong enema solution, "soapsticks," and suppositories.[2] In our experience the "laxative habit" is not restricted to the older age groups but is also a pediatric problem.

In artificially fed infants the constipation is sometimes due to the higher calcium content of cow's milk, inadequate carbohydrate, and excessive protein.[3, 4] It can often, but not always, be relieved or corrected by adjustment of the formula.

Most constipation in infants and young children is of the atonic variety. It is usually purely functional due to the repeated use of enemas and cathartics, but congenital abnormality, such as Hirschsprung's disease, malnutrition, or metabolic disorders may be involved.[5] Fortunately these latter causes are uncommon, although rickets, hyperthyroidism, thiamine deficiency, and anemia may be associated with loss of muscular tone and sluggish intestinal peristalsis.[6]

In older children constipation often accompanies a leptosome habitus, with general poor muscular development and a tendency toward lessened physical activity. In the neuropathic child the constipation is often of the "spastic" type.[1] In many children the inconvenience of leaving the schoolroom or reluctance to leave games or play results in stifling the urge to defecate. Repeated supression of the anorectal reflex causes eventual constipation.[7]

Such abnormalities as redundant mucosa or intestinal polyp may sometimes be responsible for constipation. Anorectal conditions are less common causes, although anal fissure, hemorrhoids, or a narrowed anal sphincter may be responsible.[3]

Constipation gives rise to a number of nonspecific symptoms.[8] Although seldom a serious health hazard, discomfort and a sense of "ill-feeling" make treatment most desirable. Anorexia, "belching," flatulence, and nausea accompany a distended and painful abdomen. Frequently the patient complains of lassitude, headache, "chills," or vertigo.[6] Often the hard stool is accompanied by considerable pain and tenesmus and may be blood streaked from severe irritation or anal fissure.

Dioctyl sodium sulfosuccinate, recently introduced as a fecal softener, appeared to offer several advantages over traditional agents in the treatment of constipation in infants and children. Both Wilson and Dickinson[9]

From the Driscoll Foundation Children's Hospital.

and Towsley[10] reported excellent results from its use in constipated infants and children. It is the purpose of this report to present results we have obtained with this substance in a group of fifty such patients.

MATERIALS AND METHODS

Fifty constipated infants and children ranging in age from 5 weeks to 14 years were used in the study. All were followed either in the outpatient clinics or pediatric wards of the Driscoll Foundation Children's Hospital, Corpus Christi, or the Well-Baby Clinic at Hermann Hospital and the Pediatric Neurology Clinic (Blue Bird Clinic) at the Methodist Hospital in Houston, Texas. Some had a history of persistent chronic constipation; others had an acute or subacute episode of constipation due to other medication or to inactivity resulting from immobilization and bed rest. Dioctyl sodium sulfosuccinate was given in the form of a soft gelatin capsule or as an aqueous solution.*

The initial dose varied according to the age of the patient and the severity of the constipation. In infants of one year or less the initial dose was 20 mg. a day. In the others it ranged from 25 to 100 mg. Dosage was increased or decreased promptly as based upon the results obtained in each patient and the individualized effective dose was then continued during the period of observation.

Generally, medication was given in a single dose in the 6:00 P.M. feeding to infants or at night to older children. In a few cases, however, medication was given both night and morning. The solution was always administered in milk or fruit juice to conceal its bitter taste. Medication in all patients was continued for fifteen days or more.

No attempt was made to control the diet or to establish proper habit time. The dioctyl sodium sulfosuccinate was given without the patient's knowledge; where capsules were used the patient did not know their purpose.

A daily record was kept of the number and consistency of bowel movements and of any side effects seen.

RESULTS

Infants Under 1 Year of Age.—The effective dose in nine constipated infants aged 5 weeks to 8 months was 10 mg. per day in two, 20 mg. per day in one, and 40 mg. in the other six. An anal fissure healed spontaneously during treatment in three infants. At proper dosage levels soft normal stools were passed during treatment.

Illustrative Case Report: M. M., a 7-week-old Latin-American female infant, was brought to the clinic because she would go three days without a bowel movement. The stools were hard, lumpy, and blood-streaked. Treatment with glycerine suppositories and enemas was unsuccessful, so she was placed on 1 per cent dioctyl sodium sulfosuccinate with a dose of 10 drops three times a day in her formula. On the third day she had two hard stools, but thereafter she had an average of two soft normal stools a day. There were no side effects.

Infants 1 to 3 Years of Age.—Sixteen constipated infants and children were treated. Seven were diagnosed

*Dioctyl sodium sulfosuccinate was supplied under the council-accepted brand name of Doxinate through the courtesy of Lloyd Brothers, Inc., Cincinnati, Ohio. Each soft gelatin capsule contains 20 mg. of dioctyl sodium sulfosuccinate; Doxinate solution was 1 per cent in strength. The same drug is available under other trade names.

as having chronic constipation; geophagia was present in two; convulsive disorders were present in three; and the other four were immobilized due to hydrocephalus, poliomyelitis, or meningitis.

A daily dosage of 50 mg. of dioctyl sodium sulfosuccinate was effective in twelve cases; 25 mg. was adequate in the other four. Soft normal daily stools were produced in all cases.

Illustrative Case Report: L. G., a 2½-year-old Latin-American boy, was admitted with tuberculous meningitis and complicating hydrocephalus. Under oral treatment with para-aminobenzoic acid, isoniazid, and streptomycin, he became very constipated and had to receive enemas constantly for relief. Prune juice was tried without any success. Fifty milligrams daily of dioctyl sodium sulfosuccinate was then begun. By the third day he was having an average of one soft normal stool a day.

Older Children.—Twenty-five children aged 4 to 14 years were treated. Seventeen of these were immobilized due to surgery or disease requiring bed rest. Convulsive disorders were present in seven. In one case of psychogenic megacolon, administration of dioctyl sodium sulfosuccinate seemed of definite benefit in the over-all management of the case. Soft normal daily stools resulted from the daily administration of 40 to 50 mg. of dioctyl sodium sulfosuccinate in eighteen patients, and 100 to 120 mg. in the other seven.

Illustrative Case Report: K. K., a 6½-year-old girl, was admitted with a diagnosis of petit mal automatism which was being treated with Tridione and Dilantin. She was suffering from severe constipation and headache and frequently went from three to four days or longer without a bowel movement. Mineral oil, milk of magnesia, prune juice, and enemas gave only temporary relief. Treatment with 100 mg. of dioctyl sodium sulfosuccinate resulted in daily soft normal stools, and her headache was much improved.

General Observations.—Dioctyl sodium sulfosuccinate administration usually resulted in a bowel movement by the second or third day. The first part and sometimes all of the feces passed during the first movements were hard and dry, but in subsequent bowel movements they were soft and well formed. They remained so as long as the patient received the medication.

After fifteen days' treatment, dioctyl sodium sulfosuccinate was prescribed *pro re nata* for ambulatory patients. The tendency toward constipation in this group was found to be markedly diminished as evidenced by infrequent need for the drug. Where episodes of constipation would recur, it was easily treated by giving dioctyl sodium sulfosuccinate for two or three days.

The medication in the immobilized patients was continued after the treatment period since the nursing staff preferred its routine use; they found the patients to be less irritable and appreciated the lessened need for time-consuming enemas.

Watery stools were seen in three patients prior to the reduction of dosage. It could not be determined whether this was due to the dioctyl sodium sulfosuccinate or occurred as a part of the pre-existing constipation-diarrhea cycle. No other side effects were observed.

Single daily dosage seemed to be as fully effective as was divided dosage in the few instances in which the latter was used.

DISCUSSION

Dioctyl sodium sulfosuccinate was very effective in relieving constipation, regardless of the type, in our group of patients. Results were most striking in those patients with a history of chronic constipation. The pattern of constipation in these children had probably continued because of habitual conscious or subconscious suppression of the anorectal reflex or of suppression due to pain and tenesmus.

The reflex must have been rapidly regained since most of these patients continued to have normal stools after cessation of treatment.

Our patients with chronic constipation were quite irritable, and several complained of a migraine type of headache. Correction of the constipation with dioctyl sodium sulfosuccinate appeared to eliminate the headache. In one of these the condition had been sufficiently severe to require analgesic drugs, but the need for these disappeared with correction of the constipation.

In our opinion dioctyl sodium sulfosuccinate is the first really effective physiologic aid in treating constipation in infants and young children. By a simple physicochemical action entirely on fecal material, the pattern of constipation appears to be readily broken. Furthermore, there is no irritation of the bowel, no interference with nutrition, and no "rebound constipation."

We agree fully with previous investigators[9, 10] that the use of dioctyl sodium sulfosuccinate represents a real advance in the treatment of constipation in pediatric patients.

SUMMARY

1. Excellent results were obtained in treatment of fifty constipated infants and children with dioctyl sodium sulfosuccinate.

2. The fecal softening action eliminates hard, dry feces. This seems to remove the principal cause of constipation.

3. In artificially fed infants a daily dose of 10 to 40 mg. is satisfactory. Children from 1 to 10 years of age usually require 50 to 60 mg. daily, and those over 10 years a daily dose of 100 to 120 mg. is usually satisfactory.

4. Treatment for fifteen days is often sufficient although continued use *pro re nata* in ambulatory patients or routinely in immobilized patients may be desirable.

5. Correction of constipation in children may relieve some of the annoying symptoms referable to faulty elimination.

REFERENCES

1. Bell, A. I., and Levine, M. I.: The Psychologic Aspects of Pediatric Practice. I. Causes and Treatment of Chronic Constipation, Pediatrics **14**: 259, 1954.
2. Vignec, A. J., and Mitty, V. C.: Treatment of Constipation in Infancy and Childhood, J. PEDIAT. **40**: 576, 1952.
3. Bakwin, H.: Constipation in Children, Pediat. Clin. North America, p. 127, 1956.
4. Maffia, A. J.: Treatment of Functional Constipation With Prune-Malt, Arch. Pediat. **72**: 341, 1955.
5. Sheffield, H. B.: Chronic Constipation in Children, Arch. Pediat. **7**: 135, 1953.
6. Reichert, J. L.: Constipation in Infants and Young Children, Pediat. Clin. North America, p. 527, 1955.
7. Swenson, O.: Classification and Treatment of Children With Severe Chronic Constipation, Am. J. Surg. **86**: 497, 1953.
8. Frisch, I. A.: Constipation in Children: Its Effect Upon Body Mechanisms, J. PEDIAT. **6**: 784, 1935.
9. Wilson, J. D., and Dickinson, D. G.: Use of Dioctyl Sodium Sulfosuccinate (Aerosol O.T.) for Severe Constipation, J. A. M. A. **158**: 261, 1955.
10. Towsley, H. A.: The Constipated Infant, J. Michigan M. Soc. **54**: 1064, 1955.

HEREDITARY SPHEROCYTOSIS IN THE NEONATAL PERIOD

Diagnosis, Incidence, and Treatment

Charles M. Shapiro, M.D., Aaron M. Josephson, M.D.,
Simon Rozengvaig, M.D., and Avner Kauffman, M.D.
Chicago, Ill.

HEREDITARY spherocytosis was described by Vanlair and Masius[1] in 1871, but only after Minkowski's[2] report in 1900 did this disorder become one of the most frequently recognized hereditary hemolytic diseases. Despite numerous studies, the onset of hereditary spherocytosis is difficult to ascertain, and its occurrence in the neonatal period has been reported in only thirteen documented cases.[3-14] Differentiation from other spherocytic hemolytic syndromes present, at this time of life, may necessitate complicated laboratory investigations.

Recently, we have observed a patient in whom the fully developed picture of hereditary spherocytosis appeared shortly after birth. This paper deals with the attempts to establish the diagnosis on an objective basis.

CASE REPORT

L. M., a Negro male, was born at term, following a normal pregnancy. His mother, aged 29 years, was known to have a spherocytic hemolytic anemia, first diagnosed two years prior to delivery. Two siblings and the propositus' father were clinically and hematologically normal. The hemoglobin level of the cord blood was normal (21 grams per cent); a complete blood count on the second day of life showed a hemoglobin of 15.4 grams per cent, with a red cell count of 4.2 million per cubic millimeter. The direct Coombs test was negative. However, a few spherocytes were seen in the blood film. The infant continued to gain weight normally. By the eleventh day of life the hemoglobin level was 12.6 grams per cent, and spherocytosis was quite marked. In the ensuing days he became pale, without evidence of clinical jaundice. As can be seen from Table I, the hemoglobin level fell to 5.5 grams per cent on the forty-second day and subsequently stabilized at about 8 grams per cent. Similar changes were found in the red cell counts. The reticulocyte levels were consistently elevated. Bone marrow aspiration, obtained on the forty-second day, showed marked erythrocytic hyperplasia. Hemoglobin analysis[15] was normal, and osmotic fragility studies (Table I) were compatible with the diagnosis of hereditary spherocytosis. The liver and spleen have never been palpable.

At the time of writing, the infant has been observed for seven months, with no change in the essential hematologic or physical findings.

Laboratory Investigations.—As can be found in Table I, spherocytosis became increasingly pronounced up to the eighteenth day and then persisted unchanged. The patient's fresh blood revealed an increased osmotic fragility: 50 per cent hemolysis at 0.50 per cent NaCl (control: 50 per cent

From the Department of Hematologic Research, Medical Research Institute, Michael Reese Hospital, and the Department of Pediatrics, Sarah Morris Hospital, Chicago.

The Department of Hematologic Research is supported in part by the Michael Reese Research Foundation and the Hulda B. and Maurice L. Rothschild Foundation for Scientific Research.

hemolysis at 0.44 per cent NaCl). This was much more marked after twenty-four hours' incubation at 37° C.—50 per cent hemolysis at 0.80 per cent NaCl (control: 50 per cent hemolysis at 0.48 per cent NaCl).

The fetal (F) hemoglobin level of 33.4 per cent on the forty-second day of life, as determined by the alkali denaturation technique, was within normal limits considering the age of the patient. However, persistent elevation of this component has been noted occasionally in hereditary spherocytosis.[16]

blood group tested could be demonstrated (Table 2).

Serology was negative both in the propositus and his mother.

DISCUSSION

Differential Diagnosis.—The diagnosis of hereditary spherocytosis in the newborn infant rests, besides a not always available positive family history, on the exclusion of other conditions associated with spherocytosis. One must rule out septicemia with a

TABLE I. HEMATOLOGIC DATA, L. M.

DAYS OF LIFE	1	2	11	18	23	40	42	48	80	120	220
Hb (Gm. %)	21.0	15.4	12.6	9.8	8.1	6.2	5.5	6.6	7.0	8.1	8.8
RBC (M/cu. mm.)		4.2	3.3	2.6	2.5	1.9		2.1	2.4	2.9	3.6
Spherocytes		+	++	+++	+++	+++		+++	+++	+++	+++
Reticulocytes (%)				5.7	11.2	12.9		12.6	13.6	12.9	8.2
Coombs test		neg.		neg.							
Bilirubin (mg. %)				2.5							
Bone marrow							Erythrocytic hyperplasia				
Osmotic fragility									Increased (fresh)*	Increased (incubated)†	
Hb analysis							A: 66.6% F: 33.4%				

*Control: 50% hemolysis at 0.44% NaCl.
Patient: 50% hemolysis at 0.50% NaCl.
†Control: 50% hemolysis at 0.48% NaCl.
Patient: 50% hemolysis at 0.80% NaCl.

TABLE II. IMMUNOLOGIC DATA ON BLOOD GROUP INCOMPATIBILITY*

	ABO SYSTEM	DIRECT COOMBS	ANTI-Rh ANTIBODIES		ANTI-Hr ANTIBODIES		ANTI-B HEMOLYSIN	ANTIBODIES (INDIRECT COOMBS) TO: D, C, C^w, E, c, e, M, N, S, P, Fj^a, K, Lu^a, Le^b, Jk^a
			SALINE	BLOCKING	SALINE	BLOCKING		
L. M.	B	Neg.						
Mother (E. M.)	O	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.

*Tests performed by the Michael Reese Research Foundation.

Although the mother was of blood group O, and the child of blood group B, no anti-B hemolysin was detected in the maternal serum.* Also, no evidence of immunization to any other concomitant hemolytic process,[17] and, the most frequent cause, iso-immunization due to ABO, Rh-Hr, and other blood group systems. Since in some instances spherocytes in the blood film may not be conspicuous initially, other

*We are indebted to Dr. Hugh Chaplin, Jr., for performing these tests.

nonspherocytic hemolytic syndromes must also be considered: (1) hereditary nonspherocytic hemolytic anemia[18-20]; (2) cytomegalic inclusion body disease[21-24]; (3) toxoplasmosis[25-29]; (4) congenital syphilis.[3] However, these diseases are readily differentiated by the clinical picture and proper tests. It should be emphasized that our patient had a negative serology, revealed no evidence of infection, and did not exhibit any clinical symptoms except pallor.

Spherocytosis in hemolytic disease of the newborn due to Rh incompatibility does occur,[31, 32] but is far less common than when ABO incompatibility is the cause. But except for the ABO system (mother O, child B), no blood group incompatibility could be demonstrated.

Most authors agree that such a heterospecific pregnancy may cause a hemolytic process in the newborn infant, although immunologic proof may not be obtainable. As pointed out by Zuelzer and Kaplan[33] and Robinson and associates,[34] the finding of high titers of anti-A and anti-B antibodies in the maternal sera is of little significance. Witebsky[35] has shown that when antibodies are not demonstrable in saline they may be recognized when albumin is used as the test diluent. Anti-A and anti-B hemolysins in all cases of erythroblastosis fetalis due to ABO incompatibility were reported by Crawford and co-workers[31] and by Zuelzer.[30] The latter also found positive results in 30 per cent of his controls, and concluded that the absence of such hemolysins was most significant in ruling out ABO incompatibility.

The anti-B antibody titers in our patient and in his mother, tested in saline, were normal. No anti-B hemolysin was found in the maternal serum.

It has long been postulated that spherocytes, although morphologically similar, may be due to a great variety of mechanisms,[37] and some facts supporting this theory have recently been published.[38-40] The presence of spherocytes in the peripheral blood is associated with increased osmotic fragility of the erythrocytes, regardless of the causative mechanisms. In hereditary spherocytosis the osmotic fragility can be markedly enhanced by incubating the red cells at 37° C. for twenty-four hours. The significance of this test is clearly shown by the observations of Young and associates,[41] that in patients with hereditary spherocytosis in whom spheroidicity and increased fragility were inconspicuous initially, the incubation osmotic fragility was elevated. We are not aware of any studies pertaining to incubation fragility tests in cases of ABO incompatibility. Our patient's red cells showed increased osmotic fragility in the fresh state, and that was considerably more marked after incubation.

It should also be noted that the clinical courses of ABO incompatibility and hereditary spherocytosis differ somewhat. In the former, jaundice is usually apparent in the first few days of life, spherocytes are seen in the peripheral blood film, and only rarely does splenomegaly not ensue shortly thereafter. The hemolytic process is relatively mild, and clinical and hematologic improvement occurs within a few weeks. In the few cases reported of hereditary spherocytosis in the neonatal period, icterus was usually

slight, pallor being much more prominent.[3-8, 10] However, the patients reported by Bernard and collaborators[13] and Betke[14] had definite jaundice as part of their symptom complex. Betke refers to a few other patients with icterus, but in whom no tests for blood group incompatibility had been done. The presence of splenomegaly was variable. David and Minot considered it an outstanding physical finding. Macauley and Hawksley could barely feel the splenic tip in their patients, which is not unusual in normal newborn infants. Our patient's spleen has not yet been found enlarged on palpation.

Thus the diagnosis of hereditary spherocytosis, as distinct from ABO incompatibility, is supported by the family history, increasing and persistent spherocytosis, osmotic fragility tests showing considerable enhancement upon incubation, as well as by the clinical picture. The absence of pertinent hemolysins in the maternal serum likewise favors this diagnosis.

Incidence.—Hereditary spherocytosis has long been thought to be inherited as a simple Mendelian dominant. Race[42] and Young[43] have shown a marked paucity of affected relatives when testing large families. If one is to accept such a theory, they point out that an excessively high rate of gene mutations would have to be postulated to account for those cases appearing without a family history. Also conflicting with the above theory is the established fact that, though clinically indistinguishable, hereditary spherocytosis may be the result of several factors. Prankerd and associates[40] have demonstrated that abnormalities of phosphate partition found in this disease may, in some instances, be corrected by the addition of adenosine to the cells, and in other clinically identical cases, no such correction occurs.

Hereditary spherocytosis may become symptomatic at any time in the patient's life. When the disease is manifest at birth, we believe that the responsible factors must have been operating in utero.

The occurrence of this disease in the Negro race has been reported infrequently,[44-53] and such reports have appeared only within the last eleven years. The majority of these authors express the concept that hereditary spherocytosis is rare in the Negro. As this was contrary to our clinical impression, we reviewed all cases with this diagnosis seen by our department in the past three years. In our series of thirteen cases, four were members of the Negro race. The admission of Negroes at our hospital has averaged from 16 to 21 per cent in this interval of time. Our series, although numerically small, does not reveal any significant difference in incidence between Negroes and Caucasians.

Treatment.—The hemolytic process in hereditary spherocytosis is not often severe enough to warrant transfusion. In some cases, a small blood infusion may be deemed advisable when the circulating hemoglobin level of the infant is perilously low.[3] Our patient's hemoglobin level fell to 5.5 grams per cent, but transfusions were withheld, there being no clinical symptoms. Betke's case had a serum bilirubin of 25.4 mg. per cent on the fourth day of life. He attributed this to inadequacy of the

liver in clearing the circulating bilirubin, and performed exchange transfusions in order to prevent kernicterus.

The definitive treatment of hereditary spherocytosis is splenectomy. Although the underlying red cell abnormality remains unchanged, this operation results in a clinical cure. In children and adults there is no detrimental effect to the patient when the spleen is removed. In infants there is some debate as to whether this operation may not render them more susceptible to future infections.

King and Shumacker[54] reported five cases of hereditary spherocytosis from three families, all of whom had splenectomies before the sixth month of life. Four developed meningitis in from six weeks to three years postoperatively; one died. The fifth infant died a few days after his operation, of a rapidly fatal, febrile illness. Gruber and co-workers[55] reported the death of a premature infant, 35 weeks' gestation, fourteen days postsplenectomy, of an overwhelming bacteremia. The infant had had an acute thrombocytopenia, and was operated fourteen hours after birth. Ferguson, quoted by King,[54] reported one death from tracheobronchitis a year following splenectomy, in a series of nine patients with congenital hemolytic anemia so treated. All were under 6 months of age at the time of surgery. In Newns' patient splenectomy was performed at 10 weeks of age and the infant died one month later of bronchopneumonia and suprarenal hemorrhage.

Diamond, Conrad and Schmidt, Abt, Wilson, David and Minot, Edwards and Heaton[4, 7, 8, 11, 12, 56] reported successful operations with no postoperative mortality. In thirty-seven cases of splenectomy for congenital hemolytic icterus, ten in patients younger than 7 months, Walter and Chaffin[57] noted no such dire effects in a follow-up ranging from 10 months to 13 years. A few other cases of splenectomy in infants for varied reasons have been reported.[58, 59] In none was increased susceptibility to infections noted. Only one patient in our series was under one year of age at the time of splenectomy (5 months), and after seventeen months of observation the child has remained quite well.

Although the final decision regarding this problem awaits more data, it has been our policy that any patient in whom the diagnosis of hereditary spherocytosis is established should be splenectomized even if he is under one year of age, if the clinical status requires it.

SUMMARY

A case of hereditary spherocytosis in a newborn Negro male is presented.

The methods of establishing the diagnosis of hereditary spherocytosis in the neonatal period are discussed.

Hereditary spherocytosis is due, in all probability, to multiple genetic factors, and these may be operating in utero.

The question of splenectomy in infants with hereditary spherocytosis is discussed.

REFERENCES

1. Vanlair, C., and Masius, J. C.: De la microcythémie, Bull. Acad. Roy. Méd. Belgique 5: 515, 1871.

2. Minkowski, O.: Ueber eine Hereditäre, unter dem Bilde eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, Verhandlg. Kongr. Inn. Med. **18**: 316, 1900.
3. Macauley, D.: Acholuric Jaundice in a Newborn Infant, Arch. Dis. Childhood **26**: 241, 1951.
4. Conrad, E., and Schmidt, R. E.: Congenital Hemolytic Anemia. A Case Requiring Early Splenectomy, Am. J. Dis. Child. **72**: 731, 1946.
5. Hawksley, J. C., and Bailey, U. M.: The Mean Diameter of the Erythrocytes in Acholuric Family Jaundice, and the Effects of Splenectomy, Lancet **2**: 1329, 1934.
6. Schiff, E.: Congenital Hemolytic Anemia With Normal Fragility of the Red Blood Cells, Arch. Dis. Child. **13**: 264, 1938.
7. David, J. K., and Minot, A. S.: Hemolytic Anemia in Infancy, Am. J. Dis. Child. **68**: 327, 1944.
8. Abt, A. F.: Hemolytic Disease in Infants, Am. J. Dis. Child. **60**: 812, 1940.
9. Josephs, H. W.: Studies in Hemolytic Anemia, Bull. Johns Hopkins Hosp. **62**: 25, 1938.
10. Newns, G. H.: Quoted by Macauley.[3]
11. Edwards, W. M., and Heaton, L. D.: Hypersplenism, Am. Pract. & Digest Treat. **6**: 387, 1955.
12. Diamond, L. K.: Congenital Hemolytic Anemia in Infancy and Childhood, M. Clin. North America **21**: 401, 1937.
13. Bernard, J., Boiron, M., and Estager, J.: Une grande famille hémolytique, Semaine hôp. Paris **92**: 3741, 1952.
14. Betke, K.: Icterus neonatorum gravis als Manifestation einer hereditären Sphärocytose, Ztschr. Kinderh. **78**: 359, 1956.
15. Singer, K.: Hereditary Hemolytic Disorders Associated With Abnormal Hemoglobins, Am. J. Med. **18**: 633, 1955.
16. Singer, K., Chernoff, A. I., and Singer, L.: Studies on Abnormal Hemoglobins. I. Their Demonstration in Sickle Cell Anemia and Other Hematologic Disorders by Means of Alkali Denaturation, Blood **6**: 413, 1951.
17. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 7, New York, 1953, Grune & Stratton.
18. Bruton, O. C., Crosby, W. H., and Motulsky, A. G.: Nonspherocytic Hemolytic Anemia Presenting as Hemolytic Disease of the Newborn Infant, Pediatrics **13**: 41, 1954.
19. Crosby, W. H.: Hereditary Nonspherocytic Hemolytic Anemia, Blood **5**: 233, 1950.
20. Motulsky, A. G., Crosby, W. H., and Rappaport, H.: Hereditary Nonspherocytic Hemolytic Diseases, Blood **9**: 749, 1954.
21. Margileth, A. M.: Cytomegalic Inclusion Disease, Pediatrics **15**: 270, 1955.
22. Bacala, J. C., and Burke, R. J.: Generalized Cytomegalic Inclusion Disease, J. PEDIAT. **43**: 712, 1953.
23. Mercer, R. D., Luse, S., and Gayton, D. H.: Clinical Diagnosis of Generalized Cytomegalic Inclusion Disease, Pediatrics **11**: 502, 1953.
24. France, N. E.: Inclusion Disease in Childhood, Arch. Dis. Childhood **26**: 588, 1951.
25. Beckett, R. S., and Flynn, F. J.: Toxoplasmosis, New England J. Med. **249**: 345, 1953.
26. Callahan, W. P., Russell, W. O., and Smith, M. G.: Human Toxoplasmosis, Medicine **25**: 343, 1946.
27. Gard, S., Magnusson, J. H., and Hagberg, E.: Congenital Toxoplasmosis, Acta paediat. **41**: 1, 1952.
28. Magnusson, J. H., and Wahlgren, F.: Human Toxoplasmosis, Acta path. et microbiol. scandinav. **25**: 215, 1948.
29. Zuelzer, W. W.: Infantile Toxoplasmosis, Arch. Path. **38**: 1, 1944.
30. McFarlane, M. N.: Hemolytic Disease and Congenital Disease in Siblings, Brit. M. J. **2**: 494, 1953.
31. Crawford, H., Cutbush, M., and Mollison, P. L.: Hemolytic Disease of the Newborn Due to Anti-A, Blood **8**: 620, 1953.
32. Greenwalt, T. J., and Triantaphyllopoulos, D. C.: In Vitro Studies of Red Cell Fragility in Anti-B Hemolytic Disease of the Newborn, J. Lab. & Clin. Med. **45**: 135, 1955.
33. Zuelzer, W. W., and Kaplan, E.: ABO Heterospecific Pregnancy and Hemolytic Disease, A. M. A. Am. J. Dis. Child. **88**: 319, 1954.
34. Robinson, G., Phillips, R., and Prystowsky, M.: Spherocytosis and Increased Fragility Occurring in Erythroblastosis Fetalis Associated With ABO Incompatibility, Pediatrics **7**: 164, 1951.
35. Witebsky, E.: Interrelationship Between the Rh System and the AB System, Blood (Special Issue) **2**: 66, 1948.
36. Zuelzer, W. W.: Section on "Erythroblastosis Caused by Anti-A and Anti-B," 7th M and R Research Conference, 1952.
37. Singer, K., and Motulsky, A. G.: The Developing (Coombs) Test in Spherocytic Hemolytic Anemia, J. Lab. & Clin. Med. **34**: 768, 1949.
38. Selwyn, J. G., and Dacie, J. V.: Autohemolysis and Other Changes Resulting From the Incubation of Red Cells From Patients With Congenital Hemolytic Anemia, Blood **9**: 414, 1954.

39. Young, L. E.: Hereditary Spherocytosis, Am. J. Med. **18**: 486, 1955.
40. Prankerd, T. A. J., Altman, K. I., and Young, L. E.: Abnormalities of Carbohydrate Metabolism of Red Cells in Hereditary Spherocytosis, J. Clin. Invest. **33**: 957, 1954.
41. Young, L. E., Izzo, M. J., and Platzer, R. F.: Hereditary Spherocytosis, I. Blood **6**: 1073, 1951.
42. Race, R. R.: On the Inheritance and Linkage Relationships of Acholuric Jaundice, Ann. Eugenics **11**: 365, 1942.
43. Young, L. E.: Observations on Inheritance and Heterogeneity of Chronic Spherocytosis, Tr. A. Am. Phys. **68**: 141, 1955.
44. Scherer, J. H., and Cecil, R. C.: Congenital Hemolytic Anemia in a Negro, J. Lab. & Clin. Med. **30**: 244, 1945.
45. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, 1951, Lea & Febiger.
46. Stragnell, R., and Smith, K. E.: Congenital Hemolytic Jaundice in a Negro Family, Am. J. Med. **1**: 53, 1946.
47. Goodman, E. G., and Gates, B. R.: Congenital Hemolytic Icterus in a Negro Family, Blood **2**: 480, 1947.
48. McCormack, R. R., and Simon, E. P.: Congenital Hemolytic Icterus in the Negro, Am. J. Med. **216**: 536, 1948.
49. Irby, R.: Congenital Hemolytic Anemia in Negro Brothers, J. A. M. A. **153**: 103, 1953.
50. Dacie, J. V.: The Hemolytic Anemias, Congenital and Acquired, ed. 1, New York, 1954, Grune & Stratton.
51. Butterworth, C. E., Kracke, R. R., and Riser, W. H., Jr.: Hereditary Spherocytic Anemia in the Negro, Blood **5**: 793, 1950.
52. Churg, J., and Rosenbaum, M.: Congenital Hemolytic Jaundice in a Negro Family, Am. J. M. Sc. **217**: 383, 1949.
53. Esmond, W. G., Quinn, C. L., and Peters, H. R.: Hereditary Spherocytosis in a Negro Family, A. M. A. Am. J. Dis. Child. **90**: 407, 1955.
54. King, H., and Shumacker, H. B.: Splenectomy in Infancy, Ann. Surg. **136**: 239, 1952.
55. Gruber, S., Radner, B., and Kogut, B.: Congenital Idiopathic Thrombocytopenic Purpura in a Premature Infant With Splenectomy, New York J. Med. **51**: 649, 1951.
56. Cole, W. H., Walter, L., and Limarzi, L. R.: Indications and Results of Splenectomy, Ann. Surg. **129**: 702, 1949.
57. Walter, L., and Chaffin, L.: Splenectomy in Infants and Children, Ann. Surg. **142**: 798, 1955.
58. Bogin, M., and Thurmond, J.: Hemangioma With Purpura, Thrombocytopenia and Erythrocytopenia, A. M. A. Am. J. Dis. Child. **81**: 675, 1951.
59. Hsia, D. Y., and Gellis, S. S.: Portal Hypertension in Infants and Children, A. M. A. Am. J. Dis. Child. **90**: 290, 1955.

At no period in life does the cultivation of a cheerful disposition tend more powerfully to the promotion of health, than during infancy and youth. It is a common observation, founded upon experience, that fretful and peevish children seldom thrive well; and it is amazing how soon, by mismanagement or neglect, their naturally cheerful and joyous dispositions may become impaired, or exchanged for a state of almost constant fretfulness and discontent.

A due attention to the moral education of children is seldom commenced sufficiently early. Although it is true, that many of the passions have no existence during infancy, while others may be said to be still in the bud, nevertheless, even in the cradle, the exhibition of fear, anger, resentment, jealousy, and their kindred emotions, is by no means unfrequent—and if not counteracted by a firm, prompt, and judicious management, these passions become often prematurely developed to a fearful extent—impairing the present health and comfort of the child, and sowing the seeds of discomfort and suffering, to destroy the happiness of the whole remaining period of its existence.

D. Francis Condie, on the Diseases of Children, 1871

NEONATAL HEPATITIS IN SIBLINGS

M. G. Peterman, M.D.
Milwaukee, Wis.

NEONATAL hepatitis is a general all-inclusive term, probably as satisfactory as any unless the specific etiological agent is known. There have been five cases of neonatal hepatitis in siblings reported in the literature.[1-3] I wish to present an additional two cases in each of two families seen in private practice within a period of two years. In these cases, syphilis, erythroblastosis, toxic agents, and nutritional disorders have been excluded so far as possible. All four patients showed the same liver lesions with infiltration of the portal areas, myelopoiesis, and many multinucleated giant cells. One sibling had an obliterated common duct, but the liver showed the same pathology as that of his sister. Both infants had bile in the stools. A thorough search was made for cytomegalic inclusion bodies and they were not found. We were not successful in obtaining liver biopsies on the mothers of these patients.

A review of these cases revealed a similar picture in each; namely, an early development of a progressively increasing jaundice. In Cases 1 and 2 the mother gave a history of an infectious hepatitis at 12 years of age. Following this, however, she delivered one child, her first pregnancy, with no history of jaundice or liver disease. After the third pregnancy, or the delivery of the second patient with jaundice, the mother was found to have gallstones. In Cases 3 and 4 there was no known history of jaundice in the mother. In case 4 there was a developmental defect in the biliary system. This perhaps could be due to an early infection of the liver during pregnancy with the subsequent liver damage and developmental defect. In all these cases the hepatitis could be viral in origin and the mothers were probably carriers.

Address: 411 E. Mason St.

CASE REPORTS

Case 1.—Marsha P., born July 15, 1952. This one-month old infant was admitted to Milwaukee Children's Hospital on Aug. 22, 1952, with a history of frequent bowel movements since birth. The stools were described as gray, and on three occasions contained bright red blood. Two days prior to admission she vomited some pink material and then seemed to be in a coma. She was taken to another hospital, and the mother was informed that the child was eating fine and having no diarrhea stools. On August 22 the mother noticed that the infant was not breathing normally and seemed pale. There was no history of cyanosis.

Physical examination revealed an acutely ill, pale, comatose white infant in shock, with acetone breath. The respirations were very shallow and rapid and the breath sounds harsh and depressed. The heart was normal. The abdomen was distended and no masses were palpable. She was treated with whole blood transfusions, 1/6 molar Na lactate, and glucose intravenously, but died nine hours after admission.

Laboratory studies revealed 9,800 white blood cells with 26 per cent segmented nuclei, 1 rod and staff nucleus, 5 per cent myelocytes, 4 per cent monocytes, and 64 per cent lymphocytes, 1.92 million red blood cells, 6.5 hemoglobin. Urine: albumin +, acetone +, and 10 white blood cells. The remainder of the urinalysis was negative. The Kline microscope slide and precipitation test was negative.

Significant Post-mortem Findings.—The liver weighed 135 grams and was pale and yellowish green. It was rather firm, and cut with more resistance than usual. The cut surface did not bulge and was mottled and dull brownish green.

The portal spaces were moderately enlarged and showed no significant lymphocytic infiltration. Radiating from the portal spaces there were intracellular bundles of connective tissue diffusely distributed. The liver cell cords were separated by these collagenous bundles and most of them contained a large amount of granular yellow brown pigment. Many canalieuli contained bile plugs. The ducts were not hyperplastic. A few blood-forming centers were present. There were many multinucleated giant cells. (Fig. 1.)

CASE 2.—Mary P., born Aug. 8, 1953. This patient, a sibling of Marsha P., was admitted to Milwaukee Children's Hospital at 23 days of age with the following history. The infant had a normal birth and weighed 8 pounds 10 ounces. She had been in apparent good health until 2 days before admission, when it was noticed that the stools were white and the eyes yellow. The parents were alarmed because of the similarity of the symptoms to those of a sibling who had died the year previously.

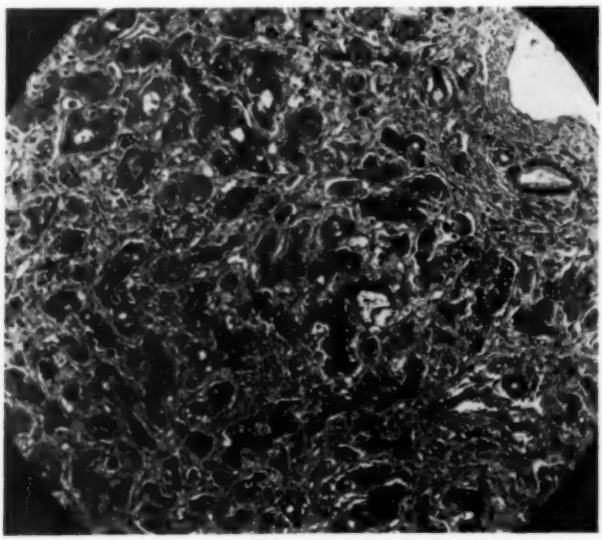


Fig. 1.

Physical examination revealed a well-developed, well-nourished, white female in no acute distress. The eyes were icteric and the liver was palpable 5 cm. below the costal margin. The stool passed during examination was of normal color and consistency, but foul in odor. Three days following admission the child was doing poorly. She started vomiting and passed changed blood per rectum. She also

started to pass deep amber urine packed with red blood cells. The bleeding tendencies continued in spite of supportive measures, which included whole fresh blood, fresh plasma, and natural and synthetic vitamin K. Seven days following admission the urinary output became deficient and she became quite edematous. She also developed an ileus at this time, which was treated unsuccessfully with prostigmine. Nine days following admission she appeared improved, the jaundice had subsided, she was less edematous, and the urine and stools were grossly free of blood. Eleven days following admission blood appeared in the stools and urine again and the respirations became irregular. Thirteen days after admission she developed pulmonary edema and started bleeding from the mouth and nose and died.

The laboratory findings are shown in Table I.

The mother was in good health throughout both pregnancies. Her past history revealed that she had infectious hepatitis at 12 years of age. There is one living child, a girl, aged 8, in good health, with no history of jaundice or liver disease. The mother was examined at the Mayo Clinic in 1953 and found to have gallstones. She had a cholecystectomy elsewhere and unfortunately a liver biopsy was not obtained.

Significant Post-mortem Findings.—The spleen weighed 28 grams and appeared to be moderately enlarged. The surface was smooth, with a few fibrous tags, and was medium red. The cut surface was darker red and the normal markings were obliterated. The pulp was firm. The liver weighed 103 grams. The capsule surface was green. The liver cut with increased resistance. The cut surface appeared jaundiced.

The liver architecture was greatly distorted by diffuse fibrosis of an excessive degree. The portal spaces were made out with some difficulty. Bile pigment was deposited heavily in the liver and Kupffer cells, away from the peripheral zone for the most part. The

TABLE I.

BLOOD

Admission Day		*Second Hospital Day*		*Fourth Hospital Day*	
WBC's	14,600	Blood sugar	93 mg.	Blood sugar	154 mg.
Seg.	50	Kline mocroppt	neg.	Prothrombin level	6%
Nonseg.	3	Blood culture	neg.		
Eos.	1				
Mono.	4				
Lymph.	42				
RBC's	4.57				
Hb. (Gm.)	16.5				

Twelfth Hospital Day		*Thirteenth Hospital Day*	
RBC's	3.16	NPN	53
Hb. (Gm.)	10	Creatinine	2.8
		Chlorides	84 meq.
		Fibrinogen	113 mg.
		Prothrombin time	5%
		Labile factor (Quick)	25% of normal
		Platelet count	4,000

URINE

Admission	*Eleventh Hospital Day*
Reaction—Alk Albumin—0 Acetone—0 RBC's—4-6 Casts—0 Sugar—+ Diacetic—0 WBC's—2-4 (Yeast fermentation showed marked fermentation, which proves presence of dextrose or fructose.)	Reaction—acid Albumin—4+ Bile—+ RBC's—packed WBC's—packed
	Stool (a) Examination was negative for excess of starch granules and fat globules. The tryptic activity was 4+.
	(b) Positive for blood.
	(c) Positive for unchanged bilirubin.

cell cords were distorted and interrupted with connective tissue growth. There was some periportal infiltration made up of neutrophils, monocytes, and lymphocytes. There were many multinucleated giant cells. Spleen: The corpuscles were atrophic. The pulp and sinuses were congested. Kidneys: The glomeruli were approximately normal, but some spaces contained albuminous precipitate. Many cortical tubules contained a similar material. The medulla was the site of inflammation, with many neutrophils in the tubules and in the interstitial tissue. (Fig. 2.)

Additional notes: The breast tissue was hyperplastic and in many parts the ducts were greatly distended.

The urine showed urobilin, but no bile. The stool was positive for unchanged bilirubin; there were 6,300 white blood cells with segmentals 27 per cent, nonsegmentals 22 per cent, metamyelocytes 3 per cent, eosinophils 2 per cent, mononuclears 6 per cent, lymphocytes 39 per cent, considerable toxic granulation; there were 4,520,000 red blood cells, 14 grams hemoglobin. The sedimentation rate was 4 mm. in one hour (Westergren); reticulocytes, 3.3 per cent; serum protein, 5.2; A:G ratio, 4:1; phosphorus, 0.3 mg.; alkaline phosphatase, 15 units (Bodansky); icterus index, 135 units; prothrombin time, 58 per cent; initial bilirubin, 9.2 mg., total 6.1; repeat study April 19, 1954, 7.1 mg. total

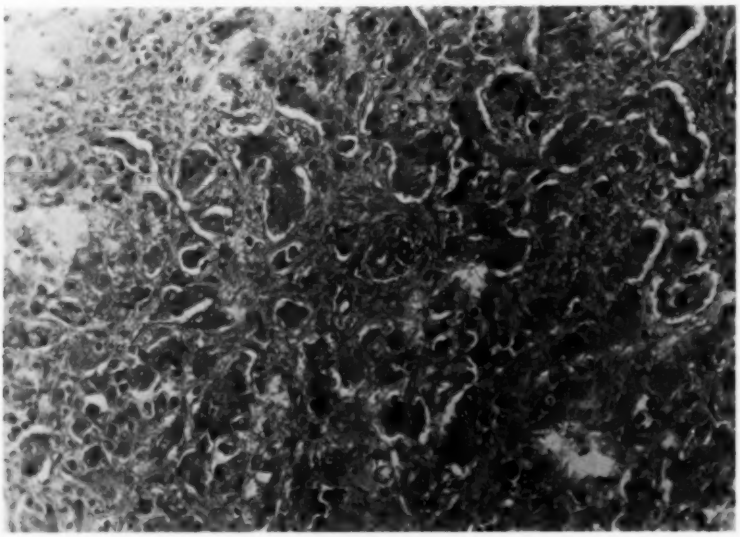


Fig. 2.

CASE 3.—A 3-week-old Indian girl, Marilyn P., had been jaundiced since 3 days of age, and had a rectal prolapse. She was a full-term normal delivery, 7 pound infant, admitted April 9, 1954. The liver was palpable 3 cm. below the right costal margin. The spleen tip was palpable 2 cm. below the left costal margin. There were Mongolian spots over the right buttock.

and 3.96 direct. Hanger's test was 4 plus. Bone marrow on April 20 showed reticulum cell hyperplasia, possibly nonlipid malignant reticuloendotheliosis. Gamma golublin was given and the globulin in the serum increased from 0.85 to 1.75 grams. The jaundice improved and disappeared completely on April 26. The liver and spleen receded in size. On May 3 the patient became jaundiced again; the total

serum bilirubin was 10.3 mg., direct 6.2 mg. A surgical exploration of the biliary tract was performed May 10. A liver biopsy showed subacute hepatitis, probably viral and secondary to hyperplastic lymphadenitis. Postoperatively, the jaundice improved slightly and the patient passed stools. The patient was discharged May 22, in poor condition and died in the Indian Hospital, Neopit, Wisconsin, June 4, 1954.

Sections of the liver, spleen, and lymph node were sent to Milwaukee Children's Hospital. Microscopic examination showed: spleen extremely congested; lymph node, reticuloendothelial cells hyperplastic; liver, giant syncytial liver cells with many nuclei. Some of these contained large fields of granular pigment which seemed to be surrounded by zones of granular material. Occasionally a solid pigment plug was seen. The Kupffer cells appeared to be filled with pigment granules. The stroma was tremendously increased, almost completely replacing the parenchyma in all areas. The bile ducts appeared moderately increased, but were not distended with bile. (Fig. 3.)

The mother was A′, Rh′ (CDe-C), antititer negative in saline, albumin. Coombs slide test was negative.

The father was O′, Rh′ Rh^2 (CDe-C) A direct Coombs test was negative.

	Thymol Turbidity	*Thymol Flocculation*	*Total Bilirubin*
Father	4.14	0	0.6
Mother	4.95	0	0.77

Case 4.—A sibling was admitted to the Wisconsin General Hospital Aug. 10, 1952, at one week of age, because of bleeding from the nose and mouth.

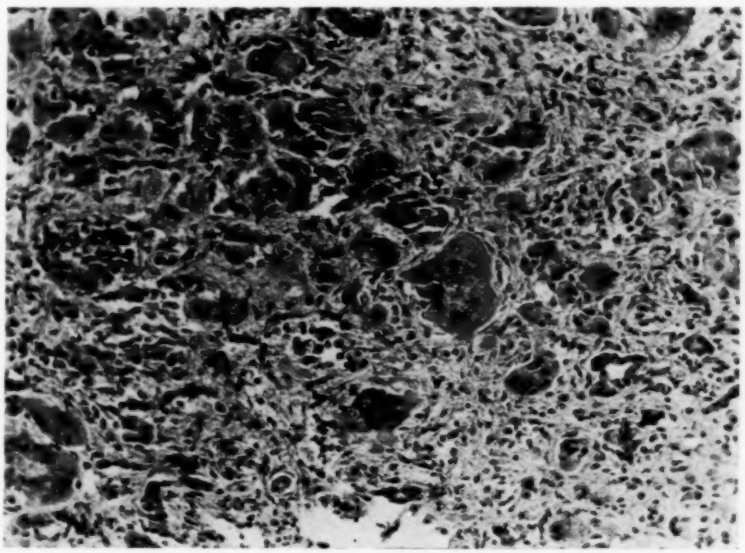


Fig. 3.

He was born Aug. 4, 1952, and weighed six pounds. He had Mongolian spots on the sacrum and jaundice of the skin and sclera. The liver was down 2 cm. below the costal margin. The blood count was normal, Coombs test negative, platelets 238,000, reticulocytes 3 per cent clot retraction poor, stool urobilinogen 2 Ehrlich units, urine negative for bile and urobilin, icterus index 33. Diagnosis: hypoprothrombinemia.

The infant was readmitted on Dec. 9, 1952, because of increasing jaun-

dice for the preceding three weeks. Examination revealed marked icterus of the skin and scleras. The liver was 4 cm. below the costal margin. The urine showed bile 4 plus, hemoglobin 5.65 grams, red blood cells 2,600,000, white blood cells 18,050, alkaline phosphatase 35 (King-Armstrong) units, bleeding time 5½ minutes, coagulation time 7¾ minutes, bilirubin direct 13, total 23, fragility normal, stool urobilinogen 2 Ehrlich units. On Dec. 13, 1952, the icterus index was 102. The infant died Dec. 14, 1952.

The post-mortem examination was performed by Dr. D. Murray Angevine.

"Post-mortem examination showed skin deeply golden in color; liver homogenous, dark green, and enlarged. the gall bladder and the cystic duct were patent. Common duct was a narrow fibrous structure with a tiny lumen above the cystoduodenal junction. The right and left hepatic ducts were present and smaller than the cystic duct, which was normal in size. Below the level of the cystic duct, the common duct lost its lumen and showed no opening into the duodenum. The ampulla was identified, but only a fibrous membrane. The liver showed coalescence of the remaining liver cells into giant cells, along with tremendous proliferation of the perilobular trabeculae into fibrous cords with compression of the liver tissue. Bile thrombi were seen and a significant proliferation of bile duct epithelium. The patient died of a purulent generalized pneumococcic meningitis." (Fig. 4.)

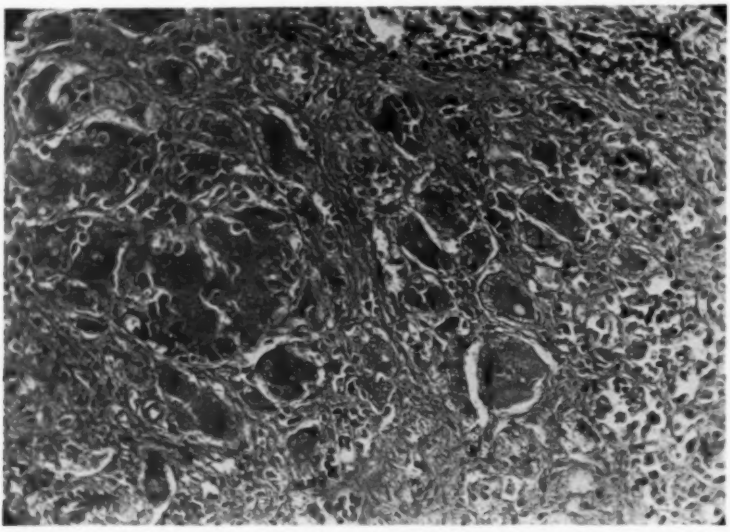


Fig. 4.

REFERENCES

1. Krainin, Philip, and Bernard, Lapan: Neonatal Hepatitis in Siblings, J.A.M.A. 160: 937, 1956.
2. Craig, John, Mand, Benj., and Landing, H.: Form of Hepatitis in Neonatal Peroid, A.M.A. Arch. Path. 54: 321, 1952.
3. Dible, J. H., and others: Foetal and Neonatal Hepatitis, J. Path. & Bact. 67: 195, 1954.

HIRSCHSPRUNG'S DISEASE IN THE NEONATAL PERIOD

A Report of Five Cases, Four of Which Involved the Small Intestine

D. H. Bowden, M.B., Ch.B., M.R.C.P. (Lond.),* A. M. Goodfellow, M.D., and J. D. Munn, M.D.
Toronto, Ontario

HIRSCHSPRUNG'S disease is due to a congenital aplasia of the myenteric plexus of the intestine. From a consideration of the developmental anatomy of the alimentary tract there is no reason to doubt the possibilities that all or part of the nerve plexus may fail to develop. There has been, however, a remarkable uniformity of pattern among the reported cases of Hirschsprung's disease. The synonym congenital megacolon presumes limitation of the aganglionic segment to the terminal portion of the large intestine and in fact the ganglionic aplasia extends proximal to the splenic flexure in less than 10 per cent of cases.[1]

The apparent constancy of this finding led Swenson and Bill[2] to postulate that the condition was due to a failure of the pelvic parasympathetic to develop, whereas the vagal innervation of the small intestine and right colon was intact. This concept has persisted and the belief is widespread that aplasia of the myenteric plexus does not involve the right colon or the small intestine. As recently as 1955 Nichols[3] stated that "Neurologic obstruction due to myenteric deficiency or early Hirschsprung's disease occurs only in the colon—usually the left."

A possible reason for this misconception is that patients with Hirschsprung's disease involving the whole of the large intestine and a variable portion of the small intestine are likely to succumb at an early age. Bodian and associates[1] reported a case in which the aganglionic segment extended to the duodenojejunal flexure. The infant died at 10 days of age. In the case described by Ehrenpreis,[4] the child died at 7 weeks. Sandegard[5] recorded the first successful treatment of long-segment Hirschsprung's disease.

In the past two years we have seen five fatal cases of Hirschsprung's disease in which the symptoms commenced in the neonatal period. Four of the patients showed ganglion aplasia of the whole of the large bowel and a portion of the small bowel.

We think that the paucity of the reports of long-segment Hirschsprung's disease in the literature reflects a lack of awareness of the existence of the condition and suggests that these cases have usually been misdiagnosed. In view of this, and

From the Departments of Pathology, Pediatrics, and Radiology of The Hospital for Sick Children and The University of Toronto.
*Present address: Cardinal Glennon Children's Hospital, St. Louis, Mo.

because the condition presents peculiar problems of diagnosis and treatment, we present our findings.

CASE REPORTS

CASE 1.—M. F., a 3-month-old female infant, was admitted with a history of constipation from birth. At 8 weeks the stools were tinged with blood and she started to vomit after meals. On admission she was wasted, the abdomen was distended and tympanitic, and masses of feces were palpated in the left colon. The anus was small and the rectum was empty.

Radiological examination with a barium meal showed poor transportation of the barium through the small bowel, with considerable segmentation. However, only a small amount of barium reached the small intestine, as most of it was vomited. The barium enema indicated that the large intestine was of normal caliber and tone; there were no constricted segments (Fig. 1, *A* and *B*).

The clinical diagnosis at this time was constipation due to anal stenosis. Daily dilatation of the anus followed by a glycerin enema was rewarded by the passage of six soft stools.

The infant was discharged but was readmitted one week later with a recurrence of symptoms. Radiological examination showed considerable distention of the small bowel with many fluid levels.

The history was considered to be strongly suggestive of Hirschsprung's disease although the earlier radiological examinations seemed to have excluded this condition. Laparotomy revealed tremendous dilatation and muscular hypertrophy of the whole small intestine except the last few inches of the ileum. The wall of the dilated intestine was purple and of

A. *B.*

Fig. 1.—*A*, Colon almost entirely outlined with barium; no evidence of a constricted segment or significant dilatation. Case 1. *B*, Postevacuation film showing good tone with fairly good evacuation of the barium; no reflux into small bowel; some distended small bowel loops seen. Case 1.

questionable viability. The cecum and colon were small and contained a few concretions. The diagnosis of Hirschsprung's disease, with the ganglion aplasia involving the large intestine and terminal ileum, was made. The condition of the child did not warrant an extensive bowel resection. She died on the following day at the age of 3½ months.

Pathology.—The clinical diagnosis was confirmed. There was complete absence of ganglion cells in the large intestine and the terminal 15 cm. of the ileum. Proximal to the obstruction the dilated and hypertrophied ileum was necrotic and infiltrated with leukocytes; no perforation had occurred. The other organs were normal; there was no evidence of fibrocystic disease of the pancreas.

CASE 2.—M. S., a 3-day-old female infant, was admitted to another hospital, with vomiting and failure to pass meconium. Laparotomy was performed, no organic obstruction was found, and the abdomen was closed. Following the operation she passed occasional small quantities of feces and the vomiting persisted. The infant was admitted to this hospital at 18 days. Radiological examination was performed. The scout film demonstrated small bowel obstruction with fluid levels and a pneumoperitoneum. The barium enema revealed the presence of a microcolon, and it was suggested that this portion of the bowel was aganglionic (Fig. 2). The condition of the child precluded further surgery and she died at 25 days.

Pathology.—The terminal ileum was perforated and the whole abdomen was a mass of friable adhesions and pockets of pus. The large intestine was of normal caliber, and contained semisolid barium and feces. The terminal 15 cm. of the ileum was narrower than the rest of the small intestine. Proximal to this segment the bowel gradually dilated but there was no severe dilatation or muscular hypertrophy.

Microscopic examination demonstrated a complete absence of ganglion cells in the large intestine and in the terminal 15 cm. of the ileum. The dilated bowel showed extensive mucosal ulceration. The pancreas was normal.

Fig. 2.—Colon presents smaller than normal caliber (microcolon). Small bowel loops appear of normal diameter for this age. Case 2.

CASE 3.—P. W. was an infant who was well at birth. Vomiting commenced at 24 hours and he was admitted at 5 days with severe abdominal distention. There was no visible peristalsis but bowel sounds were heard. Radiographic examination demonstrated distended loops of small bowel and free fluid and gas in the peritoneal cavity, indicating rupture of the bowel (Fig. 3).

Laparotomy was performed on the day of admission. The jejunum and ileum were greatly distended; the terminal 10 cm. of the ileum and the whole of the large intestine were of

smaller caliber than normal. An end-to-end ileocolic anastomosis was performed, the lower ileum and most of the cecum being resected. The abdominal distention recurred three days later and he died at the age of 13 days.

Pathology.—The ileocolic anastomosis was perforated and there was generalized peritonitis. The colon and ileum were aganglionic to a point 5 cm. proximal to the line of ileal resection. The left kidney and ureter were hypoplastic. There was no evidence of fibrocystic disease of the pancreas.

Fig. 3.—Considerable free air and fluid in abdomen indicating perforation of the intestine. Some air noted in partially filled small bowel loops; no evidence of gas in rectum. Chest clear. Case 3.

Case 4.—K. R. was a male infant normal at birth; he passed meconium but vomited most of the feedings. He was admitted at 2 days, slightly jaundiced, with abdominal distention but in no obvious distress. The anal sphincter was tight and the rectum was empty. On the day after admission he passed frequent, loose, yellow stools. The vomiting subsided and he was discharged at 7 days. Symptoms recurred shortly, however, and he was moribund on readmission at 11 days. He passed two watery stools; the abdomen was distended but not rigid.

Radiological examination was limited to a scout film of the abdomen which showed small bowel obstruction. He died at 12 days.

Pathology.—There was generalized peritonitis, but no evidence of perforation was seen. The intestine was dilated as far as the splenic flexure. The distal constricted segment was devoid of ganglion cells. There was extensive mucosal ulceration of the dilated cecum and transverse colon. The pancreas was normal.

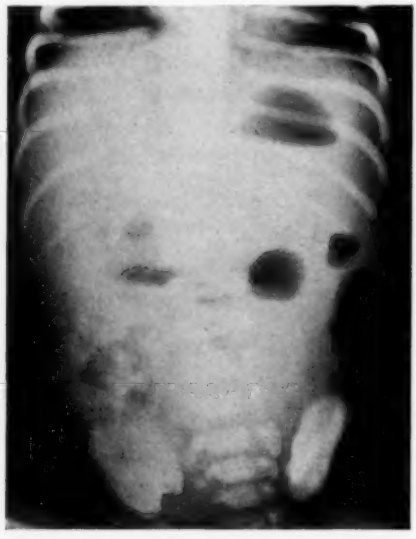


Fig. 4.—Slight distention of small bowel loops, with fluid levels seen in upright projection (fluid levels frequently seen in normal infants). Calcification in right lower quadrant; no gas in the rectum. Chest clear. Case 5.

Case 5.—L. B., a female infant, vomited dark brown fluid shortly after birth. She was admitted at 3 days. The abdomen was distended, a small

amount of meconium was passed, and she continued to vomit.

Radiological examination revealed subacute small bowel obstruction with extensive peritoneal calcification in the right lower quadrant (Fig. 4). There was no gas in the rectum. The picture was thought to represent an antenatal meconium peritonitis with calcification. The barium enema showed a microcolon.

Laparotomy on the fifth day revealed a dilated small intestine and a colon of small caliber. Meconium ileus was suspected. The infant died soon after the operation.

Pathology.—The small intestine was dilated as far as the last portion of the jejunum. The whole of the ileum and large intestine was narrow and contained hard pellets of meconium. There was stercoral ulceration of the constricted segment but no perforation was seen. The whole of this segment was aganglionic. The pancreas was normal.

DISCUSSION

Hirschsprung's disease involving a long segment of intestine is probably not uncommon. The importance of the condition as a cause of intestinal obstruction in the newborn infant is illustrated in Table I, which shows that Hirschsprung's disease and meconium ileus, associated with pancreatic fibrosis, together comprised almost half the fatal cases of intestinal obstruction in this age group.

TABLE I. INTESTINAL OBSTRUCTION IN THE NEWBORN INFANT (1953 TO 1956)

Duodenal atresia	4	
Small intestine atresia	3	
Intestinal malrotations	2	
Imperforate anus	5	
Hirschsprung's disease	5	4, long-segment
Meconium ileus (pancreatic fibrosis)	6	
Total number of autopsies	25	

The cases which we have described illustrate the difficulties of diagnosis. The presenting symptoms were vomiting and abdominal distention, meconium stools were usually passed, and one infant had an episode of diarrhea.

The radiographic findings were equally confusing, since many of the roentgenographic signs suggested meconium ileus or ileal atresia. Scout films of the abdomen showed evidence of acute small bowel obstruction, and in two cases pneumoperitoneum was present. The presence of gas in the rectum in three cases probably contradicted the diagnosis of meconium ileus and certainly excluded that of atresia of the ileum. The presence of peritoneal calcification in Case 5 was thought to indicate ante-partum perforation of the intestine consequent on meconium ileus, although no evidence of perforation was found at autopsy.

The barium enema demonstrated that in three of the five cases the colon was smaller than normal. In Case 1, however, the colon appeared to be of normal caliber and tone although the whole of the large intestine was aganglionic.

It would seem therefore that the only radiological signs of value in the diagnosis of Hirschsprung's disease in the neonatal period are pneumoperitoneum, microcolon with gas in the rectum, small bowel obstruction and calcification in the abdomen. It is often difficult to determine in a single film of the abdomen whether there is any narrowing of the large intestine, and a barium enema should therefore be performed in all cases.

The failure to recognize these cases previously means that they have probably been missed at autopsy. The

final stage of the disease when there is perforation of the ileum and generalized peritonitis is likely to be dismissed as an intestinal obstruction of unknown etiology. The recognition of five cases within three years, whereas none had been diagnosed previously, suggests that the mistake has been made.

Treatment.—If the diagnosis of long-segment Hirschsprung's disease is difficult, the treatment poses an even greater problem and at the moment it is probably true to say that in very few of these cases do the patients survive. However, the condition is not always hopeless. Sandegard[5] reported a case in which he performed total colectomy and ileo-anostomy; he stated that the child was well at the age of 2 years.

It would seem that the only reasonable immediate procedure in these cases is an ileostomy above the level of the obstruction. Radical procedures should be postponed until the child is in good condition. Removal of the whole aganglionic segment of bowel is the only rational treatment of Hirschsprung's disease, and when the segment extends into the small intestine the difficulties are obvious. It may be possible, however, as Sandegard[5] has shown, to save some of these patients.

SUMMARY

Five fatal cases of Hirschsprung's disease have been presented. Four patients died in the neonatal period and one at 3½ months. The aganglionic segment extended into the small intestine in all but one case. The problems of diagnosis, with particular reference to the radiological signs, and the difficulties of treatment have been discussed.

We wish to thank the members of the hospital staff who gave permission for these case reports to be published.

REFERENCES

1. Bodian, M., Carter, C. O., and Ward, B. C. H.: Hirschsprung's Disease, Lancet **260**: 302, 1951.
2. Swenson, O., and Bill, A. H., Jr.: Resection of Rectum and Rectosigmoid With Preservation of the Sphincter for Benign Spastic Lesions Producing Megacolon: an Experimental Study, Surgery **24**: 212, 1948.
3. Nichols, J. N.: The Differential Diagnosis of Alimentary Tract Obstructions in the Newborn, Am. J. Surg. **90**: 262, 1955.
4. Ehrenpreis, T.: Meconium Ileus and Hirschsprung's Disease, Acta paediat. **40**: 227, 1951.
5. Sandegard, E.: Hirschsprung's Disease With Ganglion Cell Aplasia of the Colon and Terminal Ileum; Report of a Case Treated With Total Colectomy and Ileo-anostomy, Acta chir. scandinav. **106**: 369, 1953.

GROWTH AND DEVELOPMENT OF NEGRO INFANTS

VIII. Comparison of the Deciduous Dentition in Negro and White Infants

(A Preliminary Study)

Angella D. Ferguson, M.D., Roland B. Scott, M.D., Washington, D.C., and Harry Bakwin, M.D., New York, N. Y.

NUMEROUS reports have appeared in anthropologic, dental, and pediatric literature pertaining to the deciduous dentition. The time of eruption of the deciduous teeth as a measure of the maturational progress of the infant is of great importance to the mother and also to the physician who must evaluate the infant's development periodically. Much has been written on the effect of diet, race, and sex on the eruption of the deciduous and permanent teeth.

This study was undertaken to compare (1) the time of eruption of the first deciduous tooth, and (2) the number of teeth present at one year of age in Negro and white infants.

METHOD

The data presented here on Negro infants were secured from two free well-baby clinics and from a private pediatric practice. These groups represented normal healthy infants from families of low and middle socioeconomic levels in the Washington, D. C., metropolitan area. A group of white infants from upper middle-income families in New York City was observed in private practice and studied in a similar manner. The method employed in the collection of data was largely of a cross-sectional nature; however, a few patients were followed longitudinally. Observations were made from 1953 through 1955.

The infants were seen at regular monthly intervals throughout the first year of life. They were breast and/or artificially fed, with supplementary vitamins added. The mothers were informed of the meaning of "eruption" of a tooth and were instructed to examine the infant's mouth regularly and record the exact date of appearance of the first tooth through the gum margin.* The interval between the date of birth and the date of eruption was computed in weeks† as the "age of eruption of the first tooth." The mothers were further instructed to count and record the number of teeth present on the infant's first birthday. The observations of the mother were confirmed by the physician's examination upon revisit to the clinic or office.

RESULTS

During the three years of this investigation (1953 through 1955), 808

From the Department of Pediatrics, Howard University College of Medicine, the Pediatric Service of Freedmen's Hospital, Washington, D. C., and the Department of Pediatrics of the College of Medicine in the New York University–Bellevue Medical Center, New York City.

*We limited our definition of an erupted tooth to its first appearance through the gum margin.

†A week was defined as seven days. Any number of days less than seven was not computed as a week.

Negro infants and 175 white infants were observed in this survey. Of the total number of Negro infants studied, 384, or 47.5 per cent, were males and 424, or 52.4 per cent, were females.

Of the total number of Negro infants, 223, or 28 per cent, were followed longitudinally, i.e., from the eruption of the first tooth through the first birthday and, therefore, are included twice in this study. Ninety-five per cent of those followed longitudinally were from the clinic group and 5 per cent were from private practice.

The results are tabulated in Table I and Figs. 1 and 2. In comparing the study groups, statistically significant* differences were found in the following categories:

1. In the Negro infants from private practice, both sexes erupted the first tooth at an earlier age than did the white infants from private practice (difference of 2.8 weeks for males and 3.9 weeks for females).

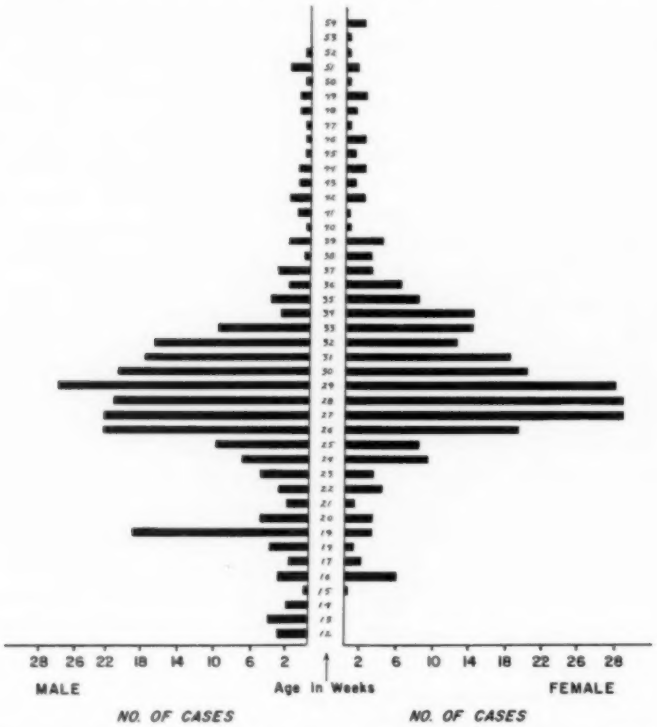


Fig. 1.—Graphic representation of the eruption age, in weeks, of the first tooth in Negro infants from clinic and private practice.

2. When the total Negro sample (clinic and private) was compared with the white infants from private practice, it was found that the Negro female infants erupted their first tooth

*The statistical test used was the "t test" (standard error of the difference between two means). The 1 per cent level was used as the level of significance.

at an earlier age (2.7 weeks) than the white females, and the white male infants had more teeth (0.9 teeth) at one year than the Negro males. (The white female infants also had more teeth than the Negro female infants at the end of one year; however, the difference was only 0.5 teeth.)

3. In comparing the two groups of Negro infants (clinic and private), significant differences were found only in the age of eruption of the first tooth, i.e., the Negro male infants from private practice erupted the first tooth 2.7 weeks earlier than the Negro males from the clinic. (The Negro

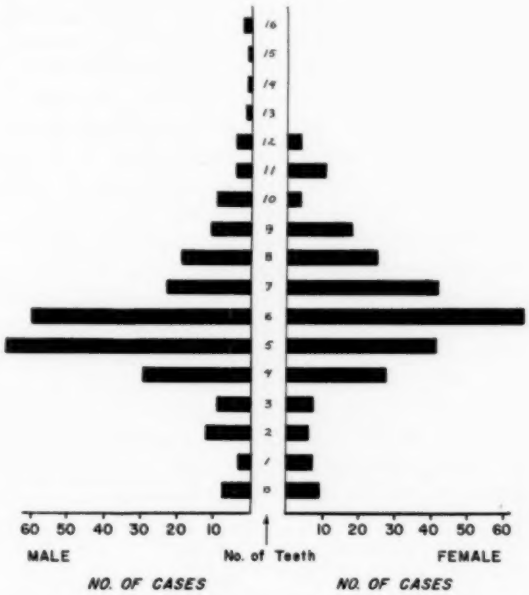


Fig. 2.—Graphic representation of the number of teeth present at 1 year of age in Negro infants from clinic and private practice.

TABLE I

	ERUPTION OF FIRST TOOTH			NUMBER OF TEETH AT ONE YEAR		
	NUMBER OF CASES	AGE IN WEEKS MEAN	AGE IN WEEKS S.D.*	NUMBER OF CASES	MEAN	S.D.*
I. Negro "clinic" infants						
Males	204	29.0	7.0	208	5.8	3.0
Females	200	29.0	8.6	214	6.1	2.6
II. Negro "private" infants						
Males	45	26.4	7.0	55	6.2	2.0
Females	52	27.7	6.7	53	5.6	2.2
III. White "private" infants						
Males	87	29.1	7.2	68	6.9	2.2
Females	88	31.6	7.5	56	6.4	2.4
IV. Negro "private" and "clinic" infants						
Males	249	27.7	7.7	263	6.0	2.8
Females	252	28.9	7.8	267	5.9	2.6

*S.D. means Standard Deviation.

female infants observed in private practice also erupted their first tooth earlier than the Negro female infants from the clinic, but the difference was only 1.3 weeks and was not statistically significant.)

COMMENT

Rhoads and associates[1] studied white and Negro children under approximately similar environmental conditions and found no striking difference in the eruption time of the deciduous teeth (7.54 and 7.78 months, respectively). However, in other studies[2, 3] of the eruption time of teeth of white and Negro races, it was found that although the differences were small, the Negro children erupted their teeth in general earlier than the white children. In the present study, too, both sexes of Negro infants from private practice erupted the first tooth at a statistically significant earlier age (difference 2.7 weeks for males and 3.9 weeks for females) than did the white infants from a similar socioeconomic level.

With respect to the white infants in our study, the males erupted their first tooth 2.5 weeks earlier than did the females (eruption ages of 29.1 and 31.6 weeks, respectively) and had 0.5 more teeth at one year of age. In other studies of white infants[4, 5] from a similar socioeconomic level, an earlier eruption age in males as compared to females was also reported. This sex difference is not found with the permanent teeth.

There are indications[6] of a relationship between the eruption of teeth and the socioeconomic status. Boas[7] found that infants from The Hebrew Home in New York City were retarded in the eruption of their deciduous teeth. These infants were inferior in general physical condition and weight to average American children at the time of admission to the home. Other workers[8] have also observed an acceleration in the eruption of the teeth when better nutritional opportunities are available.

The findings of the present study are in partial agreement with other investigators. In comparing the two groups of Negro infants from middle and low socioeconomic levels (i.e., private and clinic), the mean eruption times are earlier for the infants from the middle-class socioeconomic environment.* However, in a comparison of the combined Negro sample (middle and low socioeconomic groups) with the white infants from a middle socioeconomic level, the eruption age of first teeth for both male and female Negro infants is earlier than that found for white infants. With respect to white infants, it is also interesting to note that although the first tooth erupted at a later age, these infants had more teeth at one year (difference of 0.9 teeth in males and 0.5 teeth in females) than Negro infants.

In comparing the eruption time of the first tooth in Negro and white infants, it is possible that a natural tendency (racial or genetic) toward accelerated eruption in the Negro may compensate for unfavorable environmental (nutritional) needs.

Similarly, when the two racial groups are compared at the end of the first year of life, the nutritional advantages of the white infants will tend to overcompensate slightly for a natural genetic lag in early dentition.

*During the period of this investigation, the annual mean incomes for the two Negro groups were $4,314.00 and $2,324.00, respectively.

In this manner, the expression of nature and nurture are influenced by the time factor. For example, there was no statistically significant difference between the number of teeth present at the end of the first year in the Negro and white infants from private practice. However, the white infants from private practice had a significantly greater number of teeth at the end of the first year than the Negro infants from the clinic (low socioeconomic level).

The influence of sex is demonstrated by a slight acceleration in dentition in the male infant both with respect to the eruption of the first tooth and the number of teeth present at one year.

SUMMARY

The time of eruption of the first deciduous tooth and the number of teeth present at one year of age in Negro and white infants was compared and related to the race, socioeconomic level, and sex of the infant.

From this study the following conclusions are made:

1. The mean time of eruption of the first deciduous tooth in Negro male and female infants was 27.7 and 28.9 weeks, respectively. The white male and female infants erupted their first tooth at 29.1 and 31.6 weeks, respectively. This earlier eruption time in Negro infants is possibly due to a racial tendency toward accelerated tooth eruption in this group.

2. The Negro male and female infants had a mean of 6.0 and 5.9 teeth at the age of one year as compared to 6.9 and 6.4 teeth for white male and female infants, respectively. The larger number of teeth found in the white infants at one year of age may be attributed to nutritional advantages, since it was of statistical significance only when the white infants from a middle socioeconomic level (private practice) were compared with Negro infants from a lower socioeconomic level (clinic infants).

3. The influence of sex is demonstrated by the slight acceleration in dentition in the male infants in all groups studied.

We are indebted to Drs. Melvin E. Jenkins, Lelabelle C. Freeman, and Althea D. Kessler, of the Department of Pediatrics, Howard University College of Medicine, for assistance in the collection of data.

Dr. Ella Oppenheimer, Director of the Bureau of Maternal and Child Welfare, and Dr. K. G. Symmonds, Attending Physician of the Bureau of Maternal and Child Welfare, assisted in furnishing a portion of the clinic infants used in this study.

Dr. Bronson Price, of the Children's Bureau, Washington, D. C., gave advice in the preparation of the manuscript.

REFERENCES

1. Rhoads, T. F., Rapoport, M., Kennedy, R., and Stokes, J.: Studies on the Growth and Development of Male Children Receiving Evaporated Milk. II. Physical Growth, Dentition and Intelligence of White and Negro Children Through the First Four Years as Influenced by Vitamin Supplements, J. PEDIAT. **26**: 415, 1945.
2. Suk, V.: Eruption and Decay of Permanent Teeth in Whites and Negroes, With Comparative Remarks on Other Races, Am. J. Phys. Anthropol. **2**: 351, 1919.
3. Steggerda, M., and Hill, T. J.: Eruption Time of Teeth Among Whites, Negroes and Indians, Am. J. Orthodontics **28**: 361, 1942.
4. Gesell, A., and Thompson, H.: Psychology of Early Growth, New York, 1938, The Macmillan Co.
5. Sontag, L. W., and Reynolds, E. L.: The Fels Composite Sheet. I. A Practical Method of Analyzing Growth Progress, J. PEDIAT. **26**: 327, 1945.
6. Sandler, H. C.: The Eruption of the Deciduous Teeth, J. PEDIAT. **25**: 140, 1944.
7. Boas, F.: The Eruption of Deciduous Teeth Among Hebrew Infants, J. Dent. Research **7**: 245, 1927.
8. Clements, E. M. B., Davis, T. E., and Pickett, K. G.: Time of Eruption of Permanent Teeth in British Children in 1947-1948, Brit. M. J. **1**: 1421, 1953.

INFANTILE MYOCLONIC SEIZURES

HENRY W. BAIRD III, M.D., AND LEATRICE G. BOROFSKY, M.D.
PHILADELPHIA, PA.

THE observation that a number of patients with infantile myoclonic seizures had histories suggesting normal development prior to the time of their immunization with diphtheria, pertussis, and tetanus antigens prompted a review of our experience with this type of convulsive disorder.

It is generally recognized that the appearance of minor motor seizures early in life is associated with a poor prognosis for future mental development.[1-3] Various terms have been used to describe this serious convulsive disorder. Among these are "infantile myoclonic seizures," "lightning major convulsions," "mass myoclonic jerks," "infantile spasms," and "jackknife convulsions." In many instances the child develops slowly from birth. However, some children with infantile myoclonic seizures apparently progress normally until 5 or 6 months of age.[4] In this latter group, motor development may continue at an average, or nearly average, rate, but speech and other evidences of interpersonal relationships fail to develop. These seizures may be the clinical manifestation of a severe cerebral malformation or of a variety of pre-, para-, or postnatal insults to an immature brain.

Although hypsarhythmias may be found on the electroencephalograms of children with convulsions other than infantile myoclonic seizures and even in some children without convulsions who have other involvements of the central nervous system, they are almost always present in patients with infantile myoclonic seizures. Therefore, in order to identify the case histories of infants who might have had infantile myoclonic seizures, the reports of approximately 2,000 electroencephalograms recorded at St. Christopher's Hospital for Children for the five-year period beginning Nov. 1, 1950, were reviewed. A hypsarhythmia, which is defined as a 1 to 2 per second spike and wave pattern of high voltage prominent in all leads, was present one or more times in the records of eighty children. These patients ranged in age from 1 week to 4 years of age at the time of the first electroencephalogram. Most of these children were referred because their was a clinical suspicion of a convulsive disorder; in some of these instances additional neurological problems were also present. Fifteen had no previous history of seizures and were referred because they had other evidence of central nervous system disease. However, six of these fifteen children had a history of a convulsive disorder subsequently.

ANALYSIS OF DATA

Types of Convulsions.—Of the eighty children whose electroencephalograms showed a hypsarhythmia,

From St. Christopher's Hospital for Children and the Department of Pediatrics of Temple University School of Medicine.

seventy-one had a history of one or more convulsions. Seventeen children had only generalized grand mal seizures; one had both grand mal and simple staring petit mal; two had one-sided tonic and clonic seizures; the remaining fifty-one had either myoclonic seizures alone or combined with other manifestations of a convulsive disorder.

Early Motor Development.—Of the fifty-one patients with infantile myoclonic seizures, twenty-four had a definite history of normal motor development in early infancy. Seven of these children were remarkable in that their gross motor behavior far exceeded their performance in other fields (fine motor, personal-social, adaptive, language). Each of these seven children failed to relate to others on a level commensurate with his motor ability. These children failed to use even a few words adequately.

Age at the Onset of Infantile Myoclonic Seizures.—Of the fifty-one patients who were known to have infantile myoclonic seizures, forty-four had their first seizures prior to their first birthday. Of the remaining seven children, the onset occurred before 18 months of age.

Mental Retardation. — Forty-three of the fifty-one children with infantile myoclonic seizures had a developmental quotient of less than 50 per cent by Gesell standards. The remaining eight were so severely retarded that formal testing could not be done.

Most of the twenty-nine children who had a hypsarhythmia on their electroencephalograms but had either another type of convulsive disorder or no history of seizures were also mentally retarded. Only one child with a hypsarhythmia is known to have an I.Q. in the normal range. She had developed normally until 2 years of age, at which time she had generalized tonic and clonic convulsions associated with acute myocarditis and meningitis. This illness was believed to have been of viral origin. Her electroencephalogram showed a definite hypsarhythmia on one occasion, but is now normal. Infantile myoclonic seizures were never observed. At the age of 4 years she had an I.Q. of 80 and had a residual motor defect, spastic quadriplegia with athetosis. At 7 years her intelligence was believed to be fully average in spite of a moderately severe motor handicap. Her progress has been satisfactory in a day school for orthopedically handicapped children. She has had no seizures since her acute illness.

Association With Cerebral Palsy.—Sixteen of the fifty-one children with infantile myoclonic seizures had a demonstrable motor defect of central origin. These were as follows: quadriplegia, seven; hemiplegia, six; diplegia, two; and hypotonic cerebral palsy (atonic diplegia), one.

Eye Involvement.—Eleven of the fifty-one patients with infantile myoclonic seizures also had marked visual problems. These were as follows: totally blind, four; marked strabismus, two; cataracts, one; and optic atrophy, four.

Etiological Factors.—Presumptive etiological factors of the fifty-one children with infantile myoclonic seizures can be divided into two groups on the basis of history.

The twenty-seven children in the first group were retarded in their motor development from birth. In

three instances the causes were hereditary (phenylpyruvic oligophrenia, tuberous sclerosis, and familial mental deficiency; one infant had congenital toxoplasmosis and seven others had histories of maternal illness (bleeding during the third month of pregnancy, two; toxemia, four; poorly controlled maternal diabetes, one). Seven children had histories suggesting prolonged or difficult deliveries (difficult breech extraction, three; subdural hematoma with symptoms from birth, two; prolonged anoxia, two). The nine remaining children who were retarded in their motor development from birth did not have contributory histories. Eleven of these twenty-seven children weighed less than 4 pounds at birth; eight of the twenty-seven children had some form of cerebral palsy.

The twenty-four children in the second group appeared to have developed normally from the time of birth. Possible causative factors in this group (see Table I) were as follows: in two instances the onset followed vaccination for smallpox; two followed an encephalitis of unknown cause; one, chicken pox encephalitis; one, measles encephalitis; two, tuberculous meningitis; one, pertussis encephalitis; two, head trauma which produced subdural hematomas; and nine followed DPT immunizations.

Therapy.—Those children who had both infantile myoclonic seizures and another convulsive manifestation were routinely started on anticonvulsant therapy. Those children whose infantile myoclonic seizures were few in number were not treated. If frequent seizures occured, phenobarbital, with Dilantin added if necessary, was given. Various drugs, singly or in combinations, were prescribed for those children whose seizures did not decrease. The time spent in attempting to find an effective drug regimen was also used to help the parents to a better understanding of their child's problems.

Infantile myoclonic seizures usually disappear before the child reaches 5 years of age. Consequently, a cause-and-effect relationship between the administration of a drug and the cessation of seizures is never certain. The clinical impressions of the effects of various therapeutic agents are summarized in the following paragraphs.

Phenobarbital.—The initial daily dose of phenobarbital was calculated on the basis of 3 mg. per kilogram of body weight. This amount was increased in two weeks to 5 or 6 mg. per kilogram of body weight. Forty-two children with infantile myoclonic seizures received this drug alone for one to forty-eight months. Twenty-two of forty-two children with infantile myoclonic seizures who received this drug alone for one to forty-eight months showed significant improvement initially. However, only six of these children remained free of seizures. Four children who received phenobarbital, but who failed to respond, had no further therapy.

Diphenylhydantoin (Dilantin).—This drug was given only in combination with phenobarbital. The initial daily dose of Dilantin was calculated on the basis of 3 mg. per kilogram of body weight. This amount was increased gradually every two to four weeks until 8 to 10 mg. per kilogram of body weight was reached. Twenty-

eight children received phenobarbital and Dilantin for one to thirty-six months. Four children had no further seizures, and one other improved.

Trimethadione (Tridione).—Eleven children received Tridione in addition to phenobarbital and Dilantin in amounts up to 90 mg. per kilogram for two to nine months, without improvement. Three of these children had grand mal seizures. Five additional children who had received Tridione alone in other clinics improved when Tridione was replaced by phenobarbital alone.

3,5-Dimethyl-5-Ethyloxazolidine-2-4-Dione (Paradione).—Eight children received 20 to 90 mg. per kilogram a day of Paradione in combination with phenobarbital and Dilantin. No improvement was noted.

5,5-Diethyl-1-Methylbarbituric Acid (Gemonil).—Ten of the children received Gemonil for one to four months without benefit. The amount of Gemonil varied from 100 to 500 Gm. daily.

TABLE I. AGE OF ONSET OF INFANTILE MYOCLONIC SEIZURES IN CHILDREN WITH A HISTORY OF NORMAL MOTOR DEVELOPMENT IN EARLY INFANCY

NO.	INSULT OR ILLNESS	AGE AT TIME OF INSULT	AGE AT ONSET OF INFANTILE MYOCLONIC SEIZURES	COMMENT
1.	Vaccination (smallpox)	9 mo.	10 mo.	
2.	Vaccination (smallpox)	10 mo.	10 mo.	
3.	Encephalitis of unknown etiology	9 mo.	9 mo.	
4.	Encephalitis of unknown etiology	7 mo.	7 mo.	
5.	Encephalitis (chicken pox)	5 mo.	5 mo.	
6.	Encephalitis (measles)	13 mo.	15 mo.	
7.	Tuberculous meningitis	4 mo.	13 mo.	
8.	Tuberculous meningitis	12 mo.	12 mo.	
9.	Encephalitis (pertussis)	16 mo.	16 mo.	
10.	Subdural hematoma	5 mo.	10 mo.	Known trauma
11.	Subdural hematoma	13 mo.	16 mo.	Known trauma
12.	DPT No. 1	4 mo.	2 da. after injection	Maternal toxemia; no difficulty otherwise
13.	DPT No. 1	7 mo.	4 da. after injection	Placenta previa
14.	DPT No. 1	6 mo.	5 da. after injection	Fever and grand mal on fourth day; exact time of onset not clear
15.	DPT No. 1	7 mo.	5 da. after injection	Maternal bleeding during third month of pregnancy
16.	DPT No. 2	6 mo.	2 da. after injection	
17.	DPT No. 1	4 mo.	1 da. after injection	Grand mal seizures and fever after 12 hr.; minor seizures next day
18.	DPT No. 1	4 mo.	4 da. after injection	Grand mal seizures on third and fourth days; minor seizures began on fourth day
19.	DPT No. 1	4 mo.	2 da. after injection	
20.	DPT No. 1	9 mo.	2 da. after injection	
21.	Unknown		4 mo.	
22.	Unknown		6 mo.	
23.	Unknown		7 mo.	
24.	Unknown		7 mo.	

Methyl-Phenyl - Ethyl-Hydantoin (Mesantoin).—Eight of the children received Mesantoin for two to six months in addition to phenobarbital and Dilantin in amounts up to 8 mg. per kilogram of body weight. One child had fewer spells, but no real benefit was noted in any of the children.

Methyl-Phenyl-Succinimide (Milontin).—Fourteen of the children received Milontin for one to three months without benefit. The amount of Milontin varied from 1 to 3 Gm. daily.

*Primidone (Mysoline).**—Twelve children received 25 to 50 mg. per kilogram a day of Mysoline in combination with phenobarbital and Dilantin. Following the administration of Mysoline in amounts sufficient to cause marked drowsiness, the seizures disappeared for one to three months in ten patients. Daily maintenance of phenobarbital, Dilantin, and Mysoline failed to prevent the recurrence of seizures. The developmental ability of these children during the seizure-free interval did not improve remarkably.

*Meprobamate (Miltown)**.—Twenty-three children received Miltown either alone or in combination with phenobarbital and Dilantin for one to eighteen months after treatment with other agents had failed. Fourteen children seemed definitely improved, five of these had no further seizures. The maximum dose was 400 mg. six times a day. Nine infants, all less than 1 year of age, received Miltown alone in amounts up to tolerance. During an observation period of three months, none of these infants seemed to improve significantly.

*Acetazolamide (Diamox)**.—No improvement was noted in sixteen children who received Diamox alone (250 mg. four times daily) for one to three months.

*Asparagine**.—Fifteen children received asparagine. It was not possible to give the amount recommended by Tower[5] (50 Gm. or one fluid pint per day) to any of the children. Improvement occurred in one patient who received 25 Gm. daily for two months. His seizures did not return after he refused to take the preparation.

Ketogenic Diet.—Three children had received a ketogenic diet in other clinics. During the dehydration phase, their seizures had disappeared. These children refused the diet and again had seizures.

Air Studies.—Fourteen children had air encephalograms. Following this procedure, eight were unchanged, three were improved, one had no further seizures, and two had many more seizures than previously.

DISCUSSION†

Buchanan[6] called attention to infantile myoclonic seizures in 1946, describing them as follows: "A type of major convulsion in young infants which is frequently not recognized as such is one in which there is a sudden forward dropping of the head with

*The following drugs, which were used in this study, were supplied through the courtesy of their manufacturers: Mysoline by Ayerst Laboratories; Miltown by Wallace Laboratories; Diamox by Lederle Laboratories; and Asparagine by Merck & Company.

†Since the completion of this manuscript it has been drawn to our attention that Asal and Moro had called this type of convulsion "Blitzkraempf" (Asal, B., and Moro, E.: Jahrb. Kinderheilk. 107: 1, 1925). Their references include an article written in 1867 which described the condition (Harpin, T.: Des accès incomplets d'épilepsie, Paris, 1867, Baillière).

adduction and flexion of the arms. They are really "lightning major" convulsions. They are most common in children less than 2 years of age. They are notoriously difficult to control completely and are most often found in association with severe degrees of cerebral agenesis and mental retardation." Taylor[7] has since described them as a sudden lightning-like contraction of the flexor muscles of the trunk which may be accompanied by abrupt flexion of the arms on the chest, and flexion of the thighs on the trunk. The forearms may be retracted and the hands are pulled to either side of the head so that seizures may resemble the so-called "startle" reflex in young infants. A sharp cry may precede or accompany the seizures. The face may assume a momentary blank and shocklike expression. In some instances a sudden noise, manipulation, or feeding may precipitate the attacks, while in others attacks may occur just prior to the onset of true sleep and immediately on arousal. In some patients the seizures are almost continuous. Livingston[8] points out that infantile myoclonic seizures are mass myoclonic movements rather than the spontaneous jerky movements of the healthy newborn.

In 1950 Lennox and Davis[9] associated the 1 to 2 per second or slow spike and wave pattern on the electroencephalogram with mass myoclonic seizures in young infants. They pointed out that patients who had classical petit mal seizures had a 3 per second spike and wave pattern and emphasized that patients with the 2 per second pattern did not develop the 3 per second spike and wave as they grew older. Taylor[7] found that the electroencephalograms of patients with infantile myoclonic seizures had one basic feature, a diffuse spike and wave pattern. Livingston[8] also noted that these patients had a spike-wave pattern which occurred at frequencies slower than 3 per second. Gibbs and associates[10, 11] called this electroencephalographic abnormality a "hypsarhythmia" (*hyps* meaning mountainous) and described it as high voltage, random, slow waves and spikes in all cortical areas which may vary from moment to moment in duration and in location. These discharges may be generalized but they are never rhythmically repetitive or highly organized.[10] The record gives the impression of total disorganization of cortical voltage regulation and is the easiest of all electroencephalographic disorders to detect.[11] Illingsworth[4] has recently pointed out that mental deterioration, myoclonic seizures, and hypsarhythmia occur without apparent cause in patients who had appeared to develop normally until 6 to 9 months of age.

The evidence that DPT immunization may be a factor in the production of infantile myoclonic seizures is suggestive but not clear-cut. It is well recognized that immunization, particularly with pertussis, is a calculated risk.[12] Byers and Moll[13] have pointed out that convulsions and severe retardation may occur following immunization. It seems apparent from their published electroencephalographic tracings that hypsarhythmias were present in two of the affected children. Low[14] has shown that EEG changes may occur following immunization, but whether or not these changes can be attributed to fever alone is not

clear. Because following immunization some infants frequently have fever, irritability, and fussiness, some have convulsions without sequelae, and some have severe central nervous system lesions, it seems possible that DPT immunization could be responsible for this convulsive disorder. In nine patients of this series infantile myoclonic seizures followed DPT immunization so closely that a cause-and-effect relationship would have to be considered. In every instance the parents gave good descriptions of normal behavior previous to the immunization, using such words as bright, alert, laughs, plays, recognized people, sat up well, like "my other children." However, three of these nine children also had a history of difficulty prior to the onset of infantile myoclonic seizures. Since a date such as the time of immunization acts as a point of reference, some other cause cannot be excluded. In the present series, there are four children in the second group who were not immunized but who developed infantile myoclonic seizures at approximately the same age without known cause.

For a variety of reasons an infant may develop slowly during the first few months of life and yet fall within the average intellectual range as an adult. However, barring a cerebral insult, the I.Q. of a child whose early motor development is normal can be expected to fall within the normal range. Although it may not be clinically apparent that an illness or immunization has an encephalitic component, this association may be more frequent than is generally recognized. In the case of infants whose development appears to be adequate up to a given time, it is possible that infantile myoclonic seizures are a symptom of such an insult rather than the expression of a latent embryological defect. The latter possibility, of course, cannot be excluded.

The presumed age of developmental achievements and other clinical data acquired in retrospect are subject to the errors of all reminiscent historical data. For this reason, it would be helpful if the written reports of routine well-baby visits were clear on the following important points: (1) ability of the infant to raise his head momentarily from the prone position, which should be present virtually from the time of delivery; (2) evidence that control of the head, neck, and back continues to be adequate for the age; (3) cooing, vocalizing, playing, and socializing before 3 months of age; (4) ability to relate to his parents and the examiner; and (5) general interest in his environment.

There is a definite need for more detailed observations of handicapped children whose histories indicate normal motor development in early infancy. Many of these children continue to have motor abilities which are far better than their adaptive, language, and personal-social development. Such patients may have hearing loss, childhood psychoses, aphasia, or an infantile postencephalopathic syndrome or a cerebral maldevelopment. Since such disturbances may exist in combinations, correct appraisal is frequently difficult. In addition to repeated developmental and psychological testing, the following should be obtained:

1. Hearing tests to determine not only possible hearing loss at certain frequencies but also whether sounds are appreciated meaningfully.

2. An appraisal of the home situation to see what emotional factors are present.

3. An attempt to document the child's early motor development, particularly in relation to illnesses and immunizations.

4. An electroencephalogram to see if a hypsarhythmia is present.

5. An inquiry concerning the presence or absence of infantile myoclonic seizures.

From observations such as these it may be possible to define more adequately those handicapped children who fail to relate to their environment at a level commensurate with their motor ability.

SUMMARY

1. Fifty-one of eighty children who had a hypsarhythmia on their electroencephalogram had infantile myoclonic seizures either alone or with some other convulsive disorder.

2. The presence of infantile myoclonic seizures suggests that the child will be significantly retarded in his intellectual abilities.

3. Although meprobamate (Miltown) has shown some promise, drug therapy for the control of infantile myoclonic seizures is unsatisfactory.

4. Some infants who manifest myoclonic seizures have a history of normal motor development during early infancy. In later life the capacity of these children to relate to their environment is much more limited than are their motor abilities.

5. Although a large number of infantile myoclonic seizures seem to be prenatally determined, some would appear to have their origin in encephalopathies of various etiologies. In the latter group, pertussis immunization should be considered as an etiological possibility.

REFERENCES

1. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis, ed. 2, New York, 1949, Paul B. Hoeber, Inc., p. 180.
2. Yannet, H.: Convulsive Disorders in Children, Pediatrics **4**: 677, 1949.
3. Yannet, H.: Treatment and Prognosis of Convulsive Disorders in Children, Bull. N. Y. Acad. Med. **26**: 466, 1951.
4. Illingsworth, R. S.: Sudden Mental Deterioration With Convulsions in Infancy, Arch. Dis. Childhood **30**: 529, 1955.
5. Tower, D. B.: Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex, Neurology **5**: 113, 1955.
6. Buchanan, D.: Convulsions in Infancy and Childhood, M. Clin. North America **30**: 163, 1946.
7. Taylor, F. M.: Myoclonic Seizures in Infancy and Childhood, Texas J. Med. **46**: 647, 1952.
8. Livingston, S.: The Diagnosis and Treatment of Convulsive Disorders in Children, Springfield, Ill., 1954, Charles C Thomas.
9. Lennox, W. G., and Davis, J. P.: Clinical Correlates of the Fast and Slow Spike-Wave Electroencephalogram, Pediatrics **5**: 626, 1950.
10. Gibbs, E. L., Fleming, M. M., and Gibbs, F. A.: Diagnosis and Prognosis of Hypsarhythmia, Pediatrics **13**: 66-73, 1954.
11. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, vol. 2, Cambridge, Mass., 1952, Addison-Wesley Press, Inc.
12. Felton, H. M., and Verwey, W. F.: The Epidemiological Evaluation of a Noncellular Pertussis Antigen, Pediatrics **16**: 637-651, 1955.
13. Byers, R. K., and Moll, F. C.: Encephalopathies Following Prophylactic Pertussis Vaccine, Pediatrics **1**: 437, 1948.
14. Low, N. L.: Electroencephalographic Studies Following Pertussis Immunizations, J. PEDIAT. **47**: 35, 1955.

PREMATURE INFANT MORTALITY

J. Hicks Corey, Jr., M.D., W. W. Waddell, Jr., M.D., and
Fred N. Mitchell, M.D.
Charlottesville, Va.

THE Department of Pediatrics of the University of Virginia Hospital has reviewed its experience with premature infants on two occasions in the past.[1] In light of modifications in treatment since the last report it seems advisable to examine the results of the past seven years to ascertain any alteration in survival rates that may have occurred and, if possible, to correlate these changes with the therapeutic modifications made. The material for the present report encompasses 974 unselected infants weighing 2,500 grams or less. All live births are included regardless of weight or condition. A significant number of the infants reviewed in this report actually did not survive long enough to gain entrance to our premature nursery. The inclusion of many of these infants would seem to unfavorably weight our report in regard to nonviable infants as compared to certain other communications concerning premature mortality rates.

PREMATURE NURSERY PROCEDURES

With certain variations the routine care of premature infants follows a definite plan. All infants weighing 1,500 to 2,500 grams on admission are placed in Armstrong incubators, while the Isolette is used for those infants who weigh less than 1,500 grams or for any infant who is in poor condition. A high-moisture atmosphere is supplied for at least twenty-four hours.

On admission the infant, unless in critical condition, is weighed and placed in the proper incubator in the Trendelenburg position. As soon as possible 5 mg. of vitamin K is given by the nurse. The attending physician performs the physical examination and the gastric lavage. Feedings are withheld for at least twenty-four hours, and at the end of the desired period 5 per cent glucose in water in variable quantities is given for three feedings at three-hour intervals. If no contraindications to feeding are found, formula is begun in amounts thought suitable for the individual infant. As a rule all infants weighing less than 2,200 grams are started on lactic acid milk, while those weighing over 2,200 grams are given evaporated milk formula. Infants previously begun on lactic acid milk are graduated to evaporated milk formula before discharge from the nursery. Those infants weighing less than 1,500 grams or those whose sucking reflex or general condition is poor are fed by gavage.

Oxygen, at present, is never used routinely and, when indicated, must be ordered by the attending physician at a stated concentration for a definite period of time. The concentration is

From the Department of Pediatrics, University of Virginia School of Medicine and the University of Virginia Hospital.

regulated at 40 per cent by limiting devices but under certain circumstances higher concentrations are available for use. All infants who receive oxygen or whose birth weight was less than 1,800 grams are examined by an ophthalmologist prior to discharge.

All infants weighing less than 1,800 grams are routinely given prophylactic penicillin. An antibiotic skin ointment is applied three times weekly on all infants not in Isolettes. The use of the antibiotic ointment has almost entirely eliminated the occurrence of impetigo neonatorum in the nursery.

Feeding of premature infants poses no very real problem. Even the very small infants can be successfully fed with the various modifications of cow's milk. We know of no more easily digested mixture than lactic acid milk. It is so readily digested by even the smallest premature infants that it can be fed undiluted without fear of food intolerance, thus affording a maximum caloric intake in small volume. Our experience with acid milk covers a period of over thirty years and fully justifies our confidence in acid milk as the feeding of choice in the lower weight brackets.

Physical conditions in our premature nursery, as regards cubic space, isolation, and suspect nurseries, are distressingly inadequate as measured by present-day minimum requirements. To what extent this may have influenced survival rates cannot be determined.

RESULTS*

Table I indicates the over-all mortality rates of the present series. Those results are divided into weight groups in Table II and compared with results of previous series. It is seen that there has been a progressive decrease in the death rate in each weight group in each series, although the change in mortality is becoming less prominent. In Table III correction is made for those premature infants weighing less than 1,000 grams who are generally conceded to be previable at birth from a physiological point of view. The fate of these small infants by weight groups is shown in Table IV.

TABLE I. OVER-ALL MORTALITY BY WEIGHT GROUPS: SERIES III

WEIGHT GROUPS IN GRAMS	NUMBER OF LIVE BIRTHS	NUMBER OF DEATHS	MORTALITY PER CENT
2,500-2,001	522	13	2.5
2,000-1,501	272	25	9.2
1,500-1,001	130	54	41.5
Under 1,000	50	47	93.6
Total	974	139	

Over-all mortality—14.3 per cent.

TABLE II. MORTALITY RATE BY BIRTH WEIGHT GROUPS

SERIES	NO. WEIGHING LESS THAN 2,500 GRAMS	OVER-ALL MORTALITY	2,500-2,001 GRAMS	2,000-1,501 GRAMS	1,500-1,001 GRAMS	UNDER 1,000 GRAMS
I	432	33.8	9.5	37.9	74.6	100.0
II	484	19.4	6.1	19.8	56 4	100.0
III	974	14.3	2.3	9.2	41 5	93.6

*Where possible a comparison will be made with previous series from the University of Virginia Hospital: series I, 1925-1935; series II, 1944-1948; series III, 1949-1955.

In Table V, where the mortality rates for all premature infants are considered in regard to time of death, it is apparent that little change during the first twenty-four hours has occurred since series II. However, after this initial period it appears that the chance of infant survival is considerably improved as compared to the 1944-1948 series. The mortality rate of 2.9 per cent in those infants surviving the first twenty-four hours is extremely gratifying.

mortality rates. In this country most of the studies that bear any significance cover periods dating from the late 1940's through the early 1950's. Most of these studies span several years and fail to give any indications of the improvements in premature care which have resulted from recent advances in therapy, namely, the careful use of oxygen and the introduction of antibiotics. In order to compare the results in this institution with similar studies, several papers were selected

TABLE III. CORRECTED MORTALITY RATES, OMITTING INFANTS WEIGHING 1,000 GRAMS OR LESS

SERIES	NUMBER OF LIVE BIRTHS 2,500-1,001 GRAMS	NUMBER OF DEATHS	MORTALITY PER CENT
I	406	120	29.6
II	453	63	13.9
III	924	92	9.9

TABLE IV. MORTALITY RATE OF INFANTS WEIGHING 1,000 GRAMS OR LESS (SERIES III)

BIRTH WEIGHT GROUPS (GRAMS)	NUMBER OF LIVE BIRTHS	NEONATAL DEATHS	MORTALITY PER CENT
1,000-751	23	21	91.3
750-501	19	18	94.7
500 or less	5	5	100.0
Total	47	44	93.6

TABLE V. MORTALITY RATES DURING AND AFTER FIRST TWENTY-FOUR HOURS

SERIES	NO. WEIGHING 2,500 GRAMS OR LESS	DEATHS IN FIRST 24 HR.	MORTALITY PER CENT	NO. SURVIVALS (POST 24 HR.)	DEATHS AFTER FIRST 24 HR.	MORTALITY PER CENT
I	432	92	21.3	340	54	15.9
II	484	48	9.9	436	46	10.5
III	974	114	11.7	860	25	2.9

Table VI gives added weight to the observation that Negro premature infants have a better chance of survival in all weight groups than do white infants. It is also evident that females fare better than males. This no doubt is related to the difference in the degree of maturity for the individual race and sex.

Within the past several years there have been few reports on premature

and are summarized in Table VII. It should be pointed out that the figures of Kendall[2] are minimal values which can be expected and do not represent the experience of the author, and in the same way the figures of Dunham[3] are the maximum values of premature survival which that author was able to find in the literature from 1922 through 1952 or by personal communications of unpublished data. The

other three sets of figures indicate the experiences of the authors quoted[4-6] and cover short periods of time which fall within the limits of this report. values reported by Dunham excepting that group of infants weighing less than 1,000 grams. Inasmuch as the 21 per cent survival for the 1,000

TABLE VI. MORTALITY RATE BY BIRTH WEIGHT, RACE, AND SEX (SERIES III)

	BIRTH WEIGHT IN GRAMS					
	2,500-2,001			2,000-1,501		
SEX AND RACE	NO. OF LIVE BIRTHS	NO. OF DEATHS	MORTALITY PER CENT	NO. OF LIVE BIRTHS	NO. OF DEATHS	MORTALITY PER CENT
Males	280	10	2.8	132	20	15.2
White	161	8	5.0	84	16	19.0
Negro	119	2	1.7	48	4	8.3
Females	241	3	1.2	140	5	3.6
White	100	2	2.0	85	3	3.5
Negro	141	1	0.7	55	2	3.6
	1,500-1,001			1,000 GRAMS OR LESS		
SEX AND RACE	NO. OF LIVE BIRTHS	NO. OF DEATHS	MORTALITY PER CENT	NO. OF LIVE BIRTHS	NO. OF DEATHS	MORTALITY PER CENT
Males	73	36	49.3	23	23	100
White	45	28	62.6	12	12	100
Negro	28	8	28.6	11	11	100
Females	57	18	31.6	27	24	88.9
White	32	15	46.9	11	11	100
Negro	25	3	12.0	16	13	81.2

TABLE VII. SURVIVAL RATES AS REPORTED BY VARIOUS AUTHORS

WEIGHT (GRAMS)	BROCKWAY ET AL. 1949	MOTSAY AND HERDOCIA 1951-1955	UNIV. VIRGINIA 1949-1955	KENDALL* 1952 (MINIMUM)	DUNHAM* 1922-1952 (HIGHEST)	POTTER 1947-1952
2,500-2,001	99.7	89.7	97.5	92.0	96.0	97.5
2,000-1,501	96.5	68.9	90.8	82.0	90.0	83.7
1,500-1,001	64.5	31.3	58.5	50.0	68.0	50.0
1,000 or less	----	12.5	6.4	6.0	21.0	2.0

*Figures reported are minimum values which can be expected or highest values reported in the literature.

TABLE VIII. PREMATURE INFANTS SURVIVING WITH SERIOUS COMPLICATIONS (SERIES III)

Total number of premature infants	36		
Erythroblastotic survivals		5	
Exchange transfusion with survival			4
Deaths without exchange transfusion			2
Survival without exchange transfusion			1
Infections		8	
Diarrhea		3	
Fluid and electrolyte problems as complications of other disease		5	
Congenital anomalies		14	
Others		8	
Total number of disorders		43	

The results at the University of Virginia Hospital are well above the expected minimum values and compare most favorably with the highest gram or less group reported by Dunham was obtained from a personal communication, the material and methods are unknown to us. Because of

the physiological immaturity of such infants and because of our discouraging experience with this group, it seems somewhat unrealistic to anticipate at the present time a salvage rate of 21 per cent. As compared with the remaining three series in Table VII, it is seen that the results for the present series fall about midway between the extremes reported. The over-all mortality rate of 14.3 per cent is a reasonable figure for the time interval reviewed in this report.

Table VIII indicates the number of premature infants surviving with serious complications in series III.

DISCUSSION

It is our opinion that the improvement in premature infant mortality results from the simultaneous application of time-tested techniques and more recent innovations in premature care. The improved efficiency of nursing and nurse supervision, the more prevalent use of prophylactic antibiotics, the more rigid isolation of patients, the use of high-moisture atmosphere, the more judicious use of oxygen for infants in poor condition, the institution of the gastric lavage immediately after birth, and improved obstetrical care are the underlying reasons for the improved survival rates of premature infants in our institution. It is generally agreed that in order to increase survival expectancy, the major improvements will largely depend on prolongation of the gestational period of the infant, decreasing the incidence of toxemia of pregnancy, and the reduction of trauma during delivery. It is our feeling that little decrease in the number of deaths will be seen in those infants who survive the crucial twenty-four to forty-eight hours following birth. Any diminution that occurs will be controlled by the improvement of antibacterial therapy, better understanding of water and electrolyte balance, and refinements in surgical correction of congenital anomalies.

SUMMARY

1. Survival rates for premature infants at the University of Virginia Hospital for the years 1949-1955 are presented.

2. Prematurity remains the major cause of death.

3. Advances in controlling infection and hemorrhage have resulted in a more optimistic outlook for the survival of the premature infant.

REFERENCES

1. Waddell, W. W., Jr., Booker, A. P., and Donald, W. D.: Observations on Premature Infants Fed Mixtures of Cow's Milk, South. M. J. **43**: 337, 1950.
2. Kendall, N.: Management of the Premature Infant, M. Clin. North America **36**: 1571, 1952.
3. Dunham, E. C.: Premature Infants, ed. 2, New York, 1955, Hoeber-Harper, p. 71.
4. Brockway, G. E., Reilly, E. T., and Rice, M. M.: Premature Mortality, J. PEDIAT. **37**: 362, 1952.
5. Motsay, D., and Herdocia, F. M.: Premature Infants: Mortality and Morbidity, Guthrie Clin. Bull. **25**: 86, 1955.
6. Potter, E. L.: Maternal Factors in Prematurity, Pediat. Clin. North America, p. 517, Aug., 1954.

AGENESIS OF THE CORPUS CALLOSUM

Report of Eight Cases in Infancy

Fremont P. Koch, M.D., and Patrick J. Doyle, M.D.
Los Angeles, Calif.

CONGENITAL absence or agenesis of the corpus callosum is a rare disorder which has been described in the neurological and surgical literature but has received little attention in the pediatric literature. It is a congenital defect, first described by Reil in 1812. Since that time, over 100 cases have been reported. Savitsky and Spinelli[1] and others cited by Carpenter[2] in his excellent review of previously reported cases have stated that there is no characteristic syndrome of agenesis of the corpus callosum, and it has been thought by some that the clinical defect observed in cases of agenesis of the corpus callosum is due to associated anomalies rather than a lesion of the corpus callosum.

It is the purpose of this report to summarize eight cases of agenesis of the corpus callosum observed at the Los Angeles Childrens Hospital between 1943 and 1956. Two of these (Cases 7 and 8) were confirmed at autopsy, one case (Case 6) was visualized at operation, and the other five had the classical pneumoencephalographic criteria laid down as follows by Davidoff and Dyke[3]:

1. Marked separation of the lateral ventricles.
2. Angular dorsal margins of lateral ventricles.
3. Concave mesial borders of lateral ventricles.
4. Dilatation of caudal portions of lateral ventricles.
5. Elongation of interventricular foramina.
6. Dorsal extension and dilatation of the third ventricle.
7. Radial arrangement of the mesial cerebral sulci around the roof of the third ventricle and their extension through the zone usually occupied by the corpus callosum.

Table I is a summary of the eight cases.

In our cases, as in previous reports, mental retardation, convulsive seizures, cerebral palsy, and miscellaneous associated anomalies have been common findings.[2, 4-6]

Five showed definite mental retardation, while retardation was suspected in the other three but could not be proved because of inadequate length of observation. Three had generalized convulsions and one of these later had episodes of focal seizures. Four had definite evidence of cerebral palsy: two spastic, one athetoid, and one flaccid. In addition, in Case 6 there was questionable generalized muscle weakness. Unlike previous reports in which weakness or spasticity has frequently been unilateral,[2] our patients showed either a

From the Department of Pediatrics, School of Medicine, University of Southern California, and the Los Angeles Childrens Hospital.

TABLE

PATIENT	SEX	AGE ONSET OF SYMPTOMS	AGE OF DIAGNOSIS	INITIAL SYMPTOMS	FAMILY HISTORY OF CENTRAL NERVOUS SYSTEM DISEASE
K. B.	Female	4 mo.	4½ mo.	Large head Large anterior fontanel Convulsions	Negative
P. C.	Male	Birth	9½ mo.	Delayed development Poor feeder	Negative
R. S.	Male	Birth	10 mo.	Large head and large fontanel	Negative
D. N.	Female	1 da.	8½ mo.	Pallor Seizures Large head	A maternal cousin had seizures
S. H.	Female	1 mo.	4 mo.	Seizures, generalized	Negative
L. B.	Male	Birth	2 mo.	Large head; otherwise normal	Negative
G. S.	Male	7 mo.	18 mo. (at autopsy)	Flaccidity	Negative
H. B.	Female	2 wk.	1 mo.	Cleft palate Choked on feeding Large head	Negative

paraplegia or quadriplegia. Associated abnormalities in our series included cleft lip, cleft palate, corneal opacities, and hemangiomas. Not seen in our series, but previously reported,[2] are ocular hypertelorism, macroglossia, microcephaly, and optic atrophy.[4] As in the literature,[2] sex incidence in our cases was equal, four male and four female. Onset of symptoms occurred between birth and 7 months, which corresponds to the onset in the majority of reported cases.[2] A few cases in the literature first manifested symptoms in adult life,[4] and in several agenesis of the corpus callosum was an unsuspected and incidental finding at necropsy.

Enlargement of the head has been reported previously[1] but not stressed

I

PHYSICAL (INCLUDING ANOMALIES)	NEUROLOGICAL	SEIZURES	CEREBRAL PALSY, TYPE	MENTAL RETARDATION
Hemangioma of back of neck and right foot Head became very large	Hyperactive reflexes, especially on left Later developed tight heel chords	At 4 mo. generalized Later became left sided Often prolonged seizures	Spastic paraplegia	Yes
Dilated scalp veins Large head Large fontanel	Bilateral internal strabismus Slightly hyperactive deep reflexes Positive Macewen's sign	None	Spastic quadriplegia	Yes
Dilated scalp veins Large head Large fontanel	Hyperactive deep reflexes Internal strabismus of left eye	None	None noted	Questionable
Small for age Large head Bulging fontanel	Blood in spinal fluid first day Large head at birth	None	None noted	Yes
Poor physical development	Hypotonic; flaccidity	Generalized	Athetoid motions	Yes
?Generalized muscle weakness	Negative, except did not seem to follow light at 2 mo.	None	?Flaccidity	Questionable (only 2 mo. when expired)
Opacities of both corneas Pupils did not react to light	Bilateral positive Babinski Flaccid extremities Diminished deep reflexes	None	Flaccidity Quadriplegia	Yes
Cleft palate Glossoptosis Large head	Negative	Generalized	None noted	Questionable (only 3 mo. when expired)

as a significant finding. We were impressed by the fact that the presenting symptom in five of our eight cases was such enlargement of the head.

Embryologically, the corpus callosum is thought to be formed between the third and fifth months of gestation from a thickening of the lamina terminalis, a midline structure connecting the two cerebral hemispheres. The callosal fibers thus formed later join a fiber system from the internal aspect of each cerebral hemisphere. The corpus callosum is thought to be completely formed by the fifth fetal month. It has been suggested that the degree of arrest in development depends on the stage of fetal life in which a pathogenetic

factor is involved. Variations in failure of development from complete absence of the corpus callosum to only slight thinning of the posterior portion have been described.[1, 2]

Very little is known about the function of the corpus callosum. It has been thought to be a coordinating mechanism between the two cerebral hemispheres. The fact that there is no consistent pattern of malfunctioning of the central nervous system when the corpus callosum is absent or poorly developed would lead to the conclusion that it has no definite or consistent function; or that if it has a function, other neural pathways can take over that function when the corpus callosum is defective. Experimental ablation of the corpus callosum in monkeys has produced no consistent results.[7] The previously mentioned fact that occasionally agenesis of the corpus callosum is an incidental and unsuspected finding at autopsy also leads us to believe that it has no definite or consistent function.

There is no known treatment for agenesis of the corpus callosum, except for treatment of associated defects such as cerebral palsy and seizures.

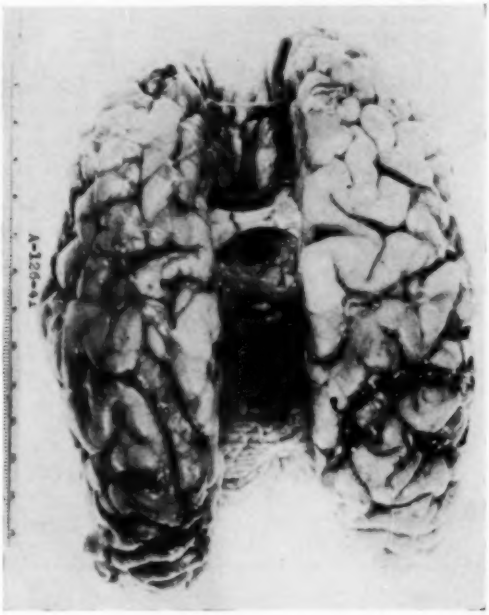


Fig 1.—Photograph of brain of G. S. (Case 7), demonstrating the absence of corpus callosum, as seen from top.

It is hoped that pediatricians may become alerted to the possibility of diagnosing agenesis of the corpus callosum by pneumoencephalography when a child has a large head, mental retardation, cerebral palsy, seizures, and/or associated congenital anomalies.

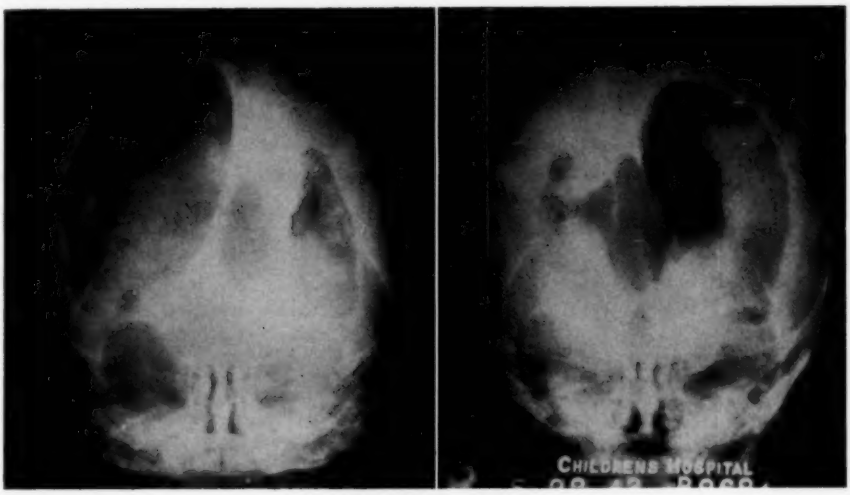


Fig. 2. Fig. 3.

Figs. 2 and 3.—Pneumoencephalogram of K. B. (Case 1), demonstrating particularly the separation of lateral ventricles, angular dorsal margin of right lateral ventricle, and dorsal extension and dilatation of third ventricle.

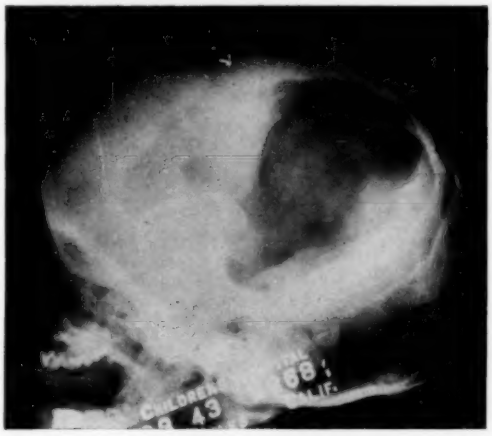


Fig. 4.—Pneumoencephalograms of K. B., showing the marked dilatation of caudal portions of left lateral ventricle.

Fig. 5.

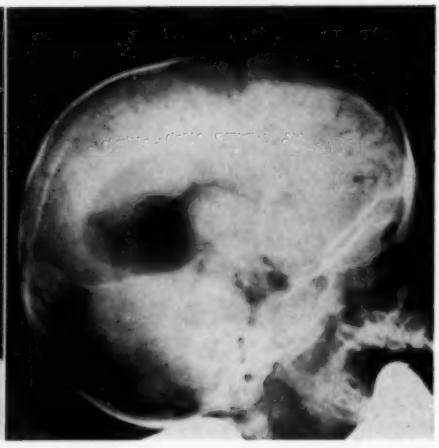


Fig. 6.

Figs. 5 and 6.—Pneumoencephalograms of R. S. (Case 3). In addition to the seven radiological criteria listed, note particularly the "bat-wing" shape of lateral ventricles (dorsal angulation and concave mesial border of lateral ventricle). The anterior fontanel is markedly enlarged.

Fig. 7.—Pneumoencephalogram of R. S., showing the fluid level because it is taken in the brow-up position.

SUMMARY

1. Eight cases of agenesis of the corpus callosum observed at Los Angeles Childrens Hospital between 1943 and 1956 have been analyzed, searching for a possible consistent clinical pattern in this condition.

2. Our findings are in agreement with those of previous observers, that there is no definite clinical syndrome in agenesis of the corpus callosum. However, in this small group of cases we were struck by the frequent occurrence of a large head, mental retardation, cerebral palsy, seizures, and the presence of other anomalies.

3. Agenesis of the corpus callosum is a rare and interesting entity which can be suspected clinically when the above findings are present and demonstrated by pneumoencephalography.

Acknowledgment is gratefully made to Drs. Arthur H. Parmelee and Robert S. Cleland, who helped in the preparation of this paper; and to Dr. John M. Clarke, who assisted in interpreting the x-rays.

REFERENCES

1. Savitsky, Elias, and Spinelli, Vincent: Agenesis of the Corpus Callosum in Infancy: Clinical and Roentgenologic Aspects, Am. J. Dis. Child. **76**: 109, 1948.
2. Carpenter, Malcolm: Agenesis Corpus Callosum Diagnosed During Life, Arch. Neurol. & Psychiat. **69**: 305, 1953.
3. Davidoff, L. M., and Dyke, C. G.: Agenesis Corpus Callosum, Am. J. Roentgenol. **32**: 1, 1934.
4. Chusid, J. G., de Gutierrez-Mahoney, C. G., and Chaffee, J. S.: Agenesis of Corpus Callosum, Arch. Neurol. & Psychiat. **62**: 840, 1949.
5. Mingazzini, G.: Der Balken, Eine anatomische, physiopathologishe und klinische Studie, Berlin, 1922, Julius Springer.
6. Baker, R. C., and Graves, G. O.: Partial Agenesis of the Corpus Callosum, Arch. Neurol. & Psychiat. **29**: 1054, 1933.
7. Kopeloff, N., and others: Section of Corpus Callosum in Experimental Epilepsy in Monkey, Arch. Neurol. & Psychiat. **63**: 719, 1950.

PURULENT NEONATAL MENINGITIS

A Study of Forty-Five Cases

David G. Watson, M.D.*
Toronto, Ontario

PURULENT meningitis in the first month of life is very different from that in older age groups as to etiology, clinical findings, and prognosis. Despite a vast reduction in over-all mortality and sequelae due to meningitis in recent years, the outlook for a newborn infant with meningitis is almost as bleak now as it was twenty-five years ago.

INCIDENCE

Estimations of the incidence of neonatal meningitis vary. Cruikshank,[1] in 1930, listed meningitis as the cause of death in thirty-three of 800 neonatal autopsies. Other estimates based on unselected autopsy material range from 0.5 to 2 per cent of neonatal deaths.[2, 3] Smith[4] states that more meningitis is seen in the first than in any other single month of life.

MATERIAL

The material for this paper consists of all cases of bacteriologically proved neonatal meningitis at the Children's Hospital of Michigan in Detroit in the five-year period ending Oct. 31, 1954, and all those at the Hospital for Sick Children, Toronto, in the six-year period ending Dec. 31, 1955. Neonatal was considered as onset within the first twenty-eight days of life. There were twenty-four such cases from Detroit and twenty-one from Toronto, not including those with meningoceles. Twenty-five of the forty-five were male. There was no seasonal incidence.

The apparent age of onset in four cases was within the first twenty-four hours of life; in thirteen cases it was between the first and seventh days; in thirteen during the second week; and in fifteen during the remainder of the neonatal period. Thirteen of the patients were premature.

Table I

TYPE OF ORGANISM	1ST DAY	1-7 DAYS	2ND WEEK	15-28 DAYS
Noncoliform	–	5	1	7
Coliform	3	11	10	8
Total (45)	3	16	11	15

In all cases the bacteriology was determined by culture of the cerebrospinal fluid, either ante or post mortem, or both, except in one case where streptococcus was grown from the blood both ante and post mortem, and seen on post-mortem smear of the brain. Coliform organisms accounted for thirty-three, or 73 per cent. There were fourteen cases due to *Escherichia coli*, ten to paracolon, three to *Bacillus proteus*, two each to *Pseudomonas pyocyaneus* and *Bacterium anitratum*, and one each to *Aerobacter aerogenes* and

From the University of Toronto.
*Present address: University of Minnesota, Department of Pediatrics, Minneapolis 14, Minn.

salmonella. Of the remainder, six cases were caused by streptococci, and one each by staphylococci, pneumococci, *Hemophilus influenzae*, meningococcus, gonococcus, and *Listeria monocytogenes*.

In a brief review of the twenty-two cases of neonatal meningitis associated with meningoceles seen at the Hospital for Sick Children, Toronto, during the same six-year period, a similar bacteriology, with a tendency to mixed infections, was noted.

TABLE II

SOURCE	ESCH. COLI	PARA-COLON	OTHER COLI-FORM	STAPH.	STREP.	PNEUMO.	OTHER	TOTAL
C.H.M.	6	6	4	1	5	–	2	24
H.S.C.	8	4	5	–	1	1	2	21
Smith	13	2	1	–	–	1	–	17
Flensborg	48	–	20	20*	32*	12	8	131
Beveridge	7	–	3	–	1	4	1	16
Debré	17	–	8	3	4	7	7	46
Total	99	12	41	24*	43*	25	20	225
		152			103			

*Some in mixed infections.

DISCUSSION OF BACTERIAL ETIOLOGY

Other series, such as Flensborg's[3] review of the literature up to 1943; Smith's[4] ten-year survey of meningitis at the Children's Hospital of Los Angeles, which included thirty-six neonates; Beveridge's[5] article which included sixteen cases of neonatal meningitis seen in a three-year period at the Royal Alexandra Hospital for Children, in Sydney, Australia; and Debré's[6] report of forty-six cases from 1946 to 1954, thirty-three from the literature and thirteen of his own; all showed a similar bacteriology.

Esch. coli and paracolon bacilli are relatively nonpathogenic organisms which rarely cause meningitis in older age groups, but in newborn infants are the commonest and deadliest offenders. A primary source of infection is often not evident, but bacteremia is nearly constant. Most of these organisms are relatively sensitive to the broad-spectrum antibiotics, but only a few cures have been reported.[7-11]

B. proteus is a common organism which rarely causes meningitis, but is difficult to treat.[12] No literature was found on meningitis due to *B. anitratum* or *A. aerogenes*, but fatal neonatal meningitis due to *B. alkaligenes* has been reported.[13]

Ps. pyocyaneus is common in the flora of some parts of the skin. Its pathogenicity is low in adults, but in children, especially infants, it is more virulent. Lately, such infections have shown an increase in actual frequency, possibly related to the widespread use of antibiotics, especially penicillin. They may be sensitive to polymyxin, neomycin, or Chloromycetin, and some cures have been reported.[14-16]

Of the 147 cases of Salmonella meningitis which Henderson[17] collected from the literature and reported in 1948, forty-nine, or one-third, were neonates, of whom only one survived. He felt that localization was influenced by diminished tissue resistance, as in

cerebral birth trauma, and also noted a tendency to epidemics in the newborn, in which diarrhea was frequent. Since 1948, Smith[18] reported six cases in neonates, with three survivors, and noted that Chloromycetin is probably the drug of choice.[18]

Meningitis due to streptococci and staphylococci is not very characteristic. Commonly it is secondary to infection elsewhere, such as omphalitis, otitis, mastoiditis, osteomyelitis, or pyoderma. Frequently meningoceles become infected by these bacteria. Hydrocephalus and hemiplegia are frequent sequelae.[19, 20]

Pneumococci are not as frequently the cause of meningitis in newborn infants as in older infants. Usually there is a primary focus of infection in the lung or ear. The pus is particularly thick, especially over the superior surfaces of the brain, and sequelae are frequent.[4, 20, 21]

Neonatal gonococcal meningitis is rare, and has been mentioned as a complication of gonococcal conjunctivitis.[22]

H. influenzae and meningococci, though the commonest causes of meningitis in infants and younger children, quite rarely cause meningitis in infants under 2 months of age.[3, 4, 9, 23] Some suggest that the rarity of these organisms in neonatal meningitis is due to transplacental transfer of antibodies.[7, 9]

L. monocytogenes is an unusual organism of definite pathogenicity, tending to produce meningitis.[24]

No report was found of a case of meningitis due to tubercle bacilli in an infant under 2 months of age.

PATHOLOGY

The pathology of neonatal meningitis is similar to that in later life, with large amounts of pus in the subarachnoid space and ventricles. The open fontanels and sutures enable the collection of large amounts of exudate without much increase in intracranial pressure, especially in premature infants.[2] There may be hemorrhage or venous thrombosis. Frequently pus collects around the base of the brain, and this, or associated arachnoiditis, may close the foramina of Lushka and Magendie, producing hydrocephalus.[11] Subdural effusions have recently been described as a complication of meningitis.[25, 26] None were noted, however, in these forty-five cases.

PREDISPOSING CONDITIONS

The early appearance of meningitis in some cases, shortly after birth, suggests prenatal or intranatal infection. Several authors mention early rupture of the membranes, prolonged or difficult deliveries, and the presence of infection (pelvic or otherwise), eclampsia, or diabetes in the mother.[3, 5, 6]

Of these forty-five cases, there were two difficult and one precipitate delivery, and two instances of early rupture of the membranes. One mother had peritonitis, one had a pneumococcal throat infection preceding pneumococcal pneumonia and meningitis in her baby, one had a marginal placenta previa, one was diabetic, two were toxemic, and two had a morbid puerperium.

That a meningocele can lead to meningitis is obvious. Other predisposing conditions in the child include cerebral birth trauma, such as subarachnoid hemorrhage, and foci of infection in the umbilicus, skin or mucous membranes, ears, lungs, etc.[3, 6, 27] In particular, the umbilicus may be

superficially healing, while the umbilical vein harbors active infection. Meningitis is often only part of a generalized septicemia, and positive blood cultures are frequent, especially in cases caused by coliform organisms. Flensborg[3] suggested that the increased permeability of the newborn's gastrointestinal mucosa is an important pathogenetic factor, noting that in his study a bacteremia was present in almost all cases due to coliform organisms. Randall[7] noted that coli agglutinins transferred from the mother to the fetus are not effective for all strains, and that neonates have poor antibody formation.

TABLE III. PREDISPOSING CONDITIONS

MATERNAL		INFANTILE	
Difficult or precipitate delivery	3	Prematurity	13
Early rupture of membranes	2	Subarachnoid hemorrhage	6
Morbid puerperium	2	Omphalitis	6
Placenta previa	1	Skin infection	3
Peritonitis	1	Peritonitis	2
Respiratory infection	1	Pneumonia	2
Toxemia	2	Otitis	3
Diabetes	1	Mastoiditis	1

Note: Sometimes two or more factors were combined.

Of these forty-five patients, six had subarachnoid hemorrhage, six had omphalitis, one impetigo, one desquamation of the skin, one cellulitis of the scalp, three otitis, two pneumonia, two peritonitis, and one mastoiditis. Sometimes more than one predisposing factor occurred in the same infant. With foci of infection, the bacteriology was usually proved to correspond to that of the meningitis.

Perhaps 40 per cent of neonatal meningitis occurs in premature infants.[1, 3] In 1949, Kagan and co-workers[28] reviewed forty-five cases from the literature, of meningitis in premature infants, including twelve cases observed during a twenty-year period at the Sarah Morris premature station in Chicago. Coliform organisms predominated. All thirteen cases of meningitis in premature infants noted in this study at Detroit and Toronto were caused by gram-negative enteric bacilli.

CLINICAL APPEARANCE

The appearance of a newborn infant with meningitis is so nonspecific that little attention is drawn to the nervous system. Usually only cerebral anoxia is suspected, such as might result from atelectasis, pneumonia, septicemia, or tetany. In many cases the diagnosis is only made at the time of post mortem.[7]

TABLE IV. SYMPTOMATOLOGY

SYMPTOM	ORDER OF OBSERVATION		
	1ST	2ND	3RD
Temperature change	14	7	3
Irritability or listlessness	11	5	1
Diarrhea	4	3	2
Vomiting or anorexia	4	9	1
Convulsion	2	6	4
Jaundice	3	1	1

Temperature change and irritability or listlessness usually occur early, and were the initial changes in fourteen and eleven cases, respectively. Subnormal temperatures were seen, as well as fever. Nine patients had diarrhea, this being the initial observation in four. Not all of these cases were due to coliform organisms. Vomiting or refusal of feedings was frequent. Eleven had cyanotic episodes and seven had some dyspnea. In only two cases was a convulsion the initial indication of meningitis. Some infants only convulsed late in the course of the disease.

On physical examination, one infant was moribund and nine were acutely ill. In four the cry was weak, and in three it was high pitched. Sixteen developed early fullness or bulging of the fontanels, and only twelve had early nuchal resistance or rigidity. These changes often developed after the diagnosis had been made. Eight were jaundiced. Spasticity, tremors, nystagmus, and other eye signs were also noted.

The white blood count ranged from 3,000 to 38,000 per cubic millimeter, but usually was 15,000 to 20,000. In the thirty-one cases with successful lumbar punctures, the fluid was always cloudy or grossly purulent, with a cell count ranging from 300 to several thousand per cubic millimeter, and the protein was elevated. Of twenty-three cases with blood cultures, nineteen were positive (fifteen for coliform organisms), three were negative (one in a case due to a coliform organism), and one grew a contaminant.

RESULTS

Of the twenty-four cases from the Children's Hospital of Michigan, fifteen infants died and thirteen were autopsied. In this same period, there were 1,035 post mortems on children up to 12 at that hospital. Two of the nine survivors are hydrocephalic (one due to *Esch. coli* and one to paracolon), and one has other evidence of cerebral damage (due to streptococcus). Of the twenty-one cases from the Hospital for Sick Children, fourteen infants died and twelve were autopsied. In the same period, 2,090 post mortems were performed on children in that hospital. Two living patients have sequelae (one due to *B. anitratum* being deaf, and the other, due to *Esch coli*, having severe hydrocephalus). Two of the "cures" were well on discharge, but their follow-up is incomplete (one was caused by *Esch. coli* and the other by *Ps. pyocyaneus*). The treatment of these infants was varied and included combinations of sulfa, penicillin, streptomycin, and the broad-spectrum antibiotics by different routes.

Thus, in the forty-five cases there was a mortality of twenty-nine, or 64 per cent, with severe sequelae in five, or 11 per cent more. The salvage was 24 per cent over-all, but only 15 per cent in the coliform group.

TABLE V. RESULTS

ORGANISM	C.H.M.			H.S.C.			COMBINED			TOTAL
	DIED	SEQ.	CURED	DIED	SEQ.	CURED	DIED	SEQ.	CURED	
Esch. coli	5	1		5	1	2	10	2	2	14
Paracolon	3	1	2	4			7	1	2	10
B. proteus	2			1			3			3
Ps. pyocyaneus	1					1	1		1	2
B. anitratum				1	1		1	1		2
A. aerogenes				1			1			1
Salmonella	1						1			1
Streptococcus	2	1	2	1			3	1	2	6
Staphylococcus	1						1			1
Pneumococcus						1			1	1
H. influenzae			1						1	1
Meningococcus				1			1			1
Gonococcus			1						1	1
L. monocytogenes						1			1	1
Total	15	3	6	14	2	5	29	5	11	45
	24			21						

TABLE VI. CASES OF NEONATAL MENINGITIS

CASE	SEX	DATE ONSET AGE ONSET	ORGANISM	CULTURES AM BLD	AM CSF	PM BLD	PM CSF	PREDISPOSING CONDITIONS	RESULTS	REMARKS
At the Hospital for Sick Children, Toronto, 1950-1955										
179014 F. R.	F	3/ 1/50 4 da.	*B. anitratum*	–	2	–	–	None	Living Deaf	Briefly feverish and anorexic; fontanel full and neck slightly stiff
180220 B. N.	M	4/26/50 6 da.	*B. anitratum*	–	–	×	×	None	Died; PM	Feverish, had GI upset; no signs
217084 D. D.	F	11/14/51 8 da.	*Esch. coli*	–	×	×	×	Premature	Died; PM	Frequent convulsions with cyanosis; no other signs
220926 G. O.	F	1/ 8/52 8 da.	*Esch. coli*	×	2	–	×	Premature Localized peritonitis	Died; PM	Fever, apathy, diarrhea, and regurgitations with cyanosis
227430 R. P.	M	3/12†/52 0-3 wk.	*Esch. coli*	–	4	–	×	None	Died; PM	Apathy and vomiting; opisthotonos, nystagmus, and hydrocephalus
238534 M. S.	F	8/12/52 1 wk.	*A. aerogenes*	–	–	×	×	Premature twin	Died; PM	Cyanotic spells, feverish
250724 R. E.	M	1/31/53 2½ wk.	Paracolon	–	×	–	–	None	Died; PM	Diarrhea, irritability, twitching; neck slightly stiff
252747 G. M.	M	3/ 1/53 10 da.	*Esch. coli*	–	2	–	×	Pneumonia Mother diabetic	Died; PM	Irritable, anorexic, 1 cyanotic spell; high-pitched cry; fontanel slightly full
254468 H. M.	M	3/24/53 2 da.	Hemolytic streptococcus	2	2	–	×	Cellulitis of scalp	Died; PM	Some twitching
259775 R. L.	M	6/ 3/53 9 da.	Paracolon	–	×	×	×	Early rupture of membranes Endometritis Otitis	Died; PM	Fever, anorexia, twitching; spasticity
263990 C. B.	F	8/ 1/53 3 wk.	*Esch. coli*	–	2	–	–	Premature twin	Cured	Fever, irritability; fontanel bulging, neck slightly stiff
264401 S. A.	F	8/ 7/53 1 wk.	*Ps. pyocyaneus*	×	×	–	–	Premature Impetigo Omphalitis	Not traced	Drowsiness; fontanel tense, neck slightly stiff; impetigo and omphalitis
266826 B. B.	F	9/24/53 2½ wk.	*Esch. coli*	–	×	–	–	Premature	Not traced	Fever, vomiting, dyspnea; dehydrated; fontanel full; head held to one side
263200 R. P.	M	10/14†/53 2 wk.†	*Esch. coli*	–	×	–	–	Premature	Died; no PM Hydrocephalic	Diarrhea, fever, convulsion; fontanel bulging

x, 1 positive culture
–, Culture negative, contaminated, or not done.
sm, Positive smear.

(*Continued on next page.*)

TABLE VI.—CONT'D

CASE	SEX	DATE ONSET AGE ONSET	ORGANISM	CULTURES AM BLD	CULTURES AM CSF	CULTURES PM BLD	CULTURES PM CSF	PREDISPOSING CONDITIONS	RESULTS	REMARKS
275251 N. A.	F	1/ 5/54 8 da.	*Esch. coli*	–	4	–	–	Premature Early rupture of membranes	Living Hydrocephalic	Fever, irritability, twitching, spasticity; fontanel full, neck slightly retracted
288122 M. D.	F	6/ 8/54 2 da.	Pneumococcus	–	×	–	–	Mother had pneumo. pharyngitis	Cured	Fever; convulsion
293834 R. W.	M	9/21/54 6 da.	*B. proteus*	–	–	–	×	Omphalitis Mastoiditis Subarachnoid hemorrhage	Died; PM	Lethargic, anorexic, icteric; neck stiff; omphalitis
296421 A. V.	M	11/ 7/54 10 da.	Paracolon	–	–	–	×	Premature Subarachnoid hemorrhages	Died; PM	Fever, vomiting, cyanosis; abdominal distention
316664 B. S.	F	10/ 8/55 24 da.	Meningococcus	–	×	–	×	Subarachnoid hemorrhage?	Died; PM	Irritability, anorexia, fever; high-pitched cry, fontanel bulging, neck slightly stiff
320045 J. W.	M	9/30/55 15 da.	Listeria monocytogenes	–	×	–	–	None	Cured	Diarrhea, irritability, fever, vomiting; fontanel full
323093 B. H.	M	11/ 7/55 4 da.	Paracolon	×	×	–	–	Desquamation of skin	Died; no PM	Dyspnea, fever
At the Children's Hospital of Michigan, Detroit, November, 1949, to October, 1954										
40804 C. H.	M	11/ 2/49 16 da.	*Esch. coli*	×	–	×	×	Otitis	Died; PM	Diarrhea, fever, icterus, convulsion; cyanosis; omphalitis?
43722 V. P.	F	1/24?/50 10 da. ?	*Esch. coli*	2	×	–	–	Premature Marginal placenta previa	Died; PM	Cyanosis, tremors, nystagmus, fever, icterus
48062 D. T.	M	3/11/50 4 da.	*Esch. coli*	×	×	–	–	None	Living Hydrocephalic	Irritability, icterus, fever, convulsion
49073 P. R.	M	5/21/50 18 da.	*Esch. coli*	×	×	×	×	Subarachnoid hemorrhage	Died; PM	Fever, anorexia, dyspnea, irritability; fontanel slightly bulging
C. H.	M	7/ 7/50 6 da.	*B. proteus*	–	–	–	×	Omphalitis Peritonitis	Died; PM	Listlessness, convulsion with cyanosis, fever; high-pitched cry
52172 G. B.	F	8/ 1/50 7 da.	Paracolon	×	2	–	–	Premature Mongoloid	Died No PM	Fever, convulsion; fontanel full
53880 B. L.	F	9/12/50 4 da.	*B. proteus*	×	–	×	×	Premature Omphalitis Subarachnoid hemorrhage	Died; PM	Irregular respirations, moderate dehydration

54673 C. F.	F	10/ 3/50 6 da.	Paracolon	×	5	–	–	None	Cured	Fever, irritability, cyanosis; nystagmus
58017 R. H.	M	1/ 3/51 9 da.	Paracolon	×	×	–	–	None	Died; PM	Fever, diarrhea, convulsion
72061 D. R.	M	11/30/51 Newborn†	Paracolon	×	×	–	–	Twin; difficult delivery	Died	Feverish, later convulsed and became icteric
78034 R. O.	M	4/14/52 Newborn†	Paracolon	×	×	–	–	None	Cured	Fever, convulsions
93996 R. H.	F	4/28/53 17 da.	Gonococcus	–	×	–	–	None	Cured	Diarrhea, fever, vomiting; fontanel bulging; purulent nasal exudate
96604 D. T.	F	6/31/53 27 da.	Hemolytic streptococcus	–	×	–	–	None	Living; brain atrophy	Irritability, vomiting, twitching; weak cry
97133 S. Mc.	F	7/ 1/53 18 da.	Paracolon	–	×	–	–	Maternal toxemia and peritonitis	Living; hydrocephalic	Fever, anorexia, convulsion
96974 H. K.	M	7/ 6/53 28 da.	Hemolytic streptococcus	–	×	–	–	Maternal toxemia	Cured	Fever, convulsion; dyspnea; fontanel slightly bulging
98084 M. H.	F	8/ 2/53 Newborn†	*Esch. coli*	×	4	–	×	Difficult delivery	Died; PM	Fever, anorexia, icterus
103984 B. H.	M	12/ 6/53 2 da.	Streptococcus	×	–	×	sm.	None	Died; PM	Fever, diarrhea, anorexia, convulsion, cyanosis; weak cry, dyspnea
112123 J. B.	M	5/ 8/54 24 da.	*H. influenzae*	–	×	–	–	Otitis	Cured	Fever, irritability, spasticity; fontanel full
112196 E. Z.	M	5/ 9/54 5 da.	Hemolytic streptococcus	–	×	–	–	None	Cured	Fever, slight icterus
110957 E. B.	F	5/20/54 27 da.	*Staph. aureus*	–	–	–	×	Morbid puerperium	Died; PM	Dyspnea, convulsion; lethargic; fontanel slightly bulging
113848 M. W.	M	6/18/54 11 da.	*Salmonella enteritidis*	–	–	×	×	Precipitate delivery Subarachnoid hemorrhages	Died; PM	Lethargy; no diarrhea; dead on arrival
115606 G. B.	F	7/11/54 Newborn†	*Ps. pyocyaneus*	×	×	×	×	Omphalitis Aspiration pneumonia	Died; PM	Cyanosis, icterus, convulsion; spasticity, weak cry, neck retraction; unequal pupils
115605 B. Mc.	M	7/23/54 9 da.	*Esch. coli*	–	–	×	×	Prematurity	Died; PM	Fever; death unexpected
119810 R. S.	M	9/28/54 10 da.	Hemolytic streptococcus	–	×	–	–	Omphalitis Neonatal hepatitis	Died; PM	Anorexia, icterus, fever; listless, weak cry, fontanel bulging; umbilical discharge

SUMMARY

Forty-five bacteriologically proved cases of purulent neonatal meningitis were described. The etiology was predominantly coliform. Various obstetrical difficulties, prematurity, and foci of infection in the infant were sometimes associated. Bacteremia usually occurred. The onset was insidious, and the clinical appearance was not at all characteristic. The only constant changes were in the spinal fluid.

It should be stressed that early diagnosis depends on a high index of suspicion coupled with a liberal use of the lumbar puncture needle. Even in recent years the results are poor, but with early vigorous therapy particularly aimed at the gram-negative bacilli, and specifically modified as indicated by culture and sensitivity testing, better results may be possible.

I wish to acknowledge my sincere appreciation to Dr. W. W. Zuelzer of the Children's Hospital of Michigan, Detroit, and to Dr. A. L. Chute, of the Hospital for Sick Children, Toronto, for the privilege of using these cases, and to Drs. T. E. Roy and C. S. Anglin of the Hospital for Sick Children, who also extended kind assistance.

REFERENCES

1. Cruikshank, J. N.: The Causes of Neonatal Death, Med. Research Council, Special Report Series No. 145, London, 1930.
2. Morison, J. E.: Foetal and Neonatal Pathology, St. Louis, 1952, The C. V. Mosby Co.
3. Flensborg, E. W.: Acute Purulent Meningitis of the Newborn, Acta paediat. **30**: 305, 1943.
4. Smith, E. S.: Purulent Meningitis in Infants and Children, J. PEDIAT. **45**: 425, 1954.
5. Beveridge, J.: Purulent Meningitis in Infants and Children, Med. J. Australia **1**: 25, 1954.
6. Debré, R.: Les meningites purulentes du nouveau-né, Semaine hôp. Paris, p. 319, Dec. 22, 1954.
7. Randall, K.: Suppurative Meningitis in the Newborn due to Coliform Bacilli, J. Clin. Path. **1**: 150, 1948.
8. Fisch, G. H.: A Case of E. coli Meningitis in Newborn Treated With Intrathecal Chloramphemicol, Guy's Hosp. Rep. **102**: 229, 1953.
9. Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children With Special Reference to Age-Incidence and Bacteriological Diagnosis, J. PEDIAT. **2**: 696, 1933.
10. Barrett, G. S., Rammelkamp, C. H., and Worcester, J.: Meningitis due to Escherichia Coli, Am. J. Dis. Child. **63**: 41, 1942.
11. Neal, J. B.: Meningitis Caused by Bacilli of the Colon Group, Am. J. M. Sc. **172**: 740, 1926.
12. Neal, J. B.: The Genus Proteus in Meningitis, Am. J. M. Sc. **174**: 665, 1927.
13. Whartin, R. O.: Alkaligenes Faecalis Meningitis Complicated by Hydrocephalus in a Premature Twin, Am. J. Dis. Child. **84**: 729, 1952.
14. Knight, V., Hardy, R. C., and Negrin, J., Jr.: Meningitis due to Pseudomonas aeruginosa, J. A. M. A. **149**: 1395, 1952.
15. Ditkowsky, S., Goldman, A., and Goldin, M.: Pseudomonas Meningitis in an Infant Successfully Treated With Neomycin, Pediatrics **9**: 101, 1952.
16. Stanley, M.: Bacillus Pyocyaneus Infections, Am. J. Med. **2**: 253, 347, 1947.
17. Henderson, L. L.: Salmonella Meningitis: Report of 3 Cases and Review of 147 Cases From Literature, Am. J. Dis. Child. **75**: 351, 1948.
18. Smith, E. S.: Salmonella Meningitis in Infancy, Am. J. Dis. Child. **88**: 732, 1954.
19. Gibel, H., and Litvak, A. M.: Hemolytic Streptococcus Meningitis in Infants Under Three Months of Age, Am. J. Dis. Child. **66**: 43, 1943.
20. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood, and Adolescence, Springfield, Ill., 1952, Charles C Thomas, p. 530.
21. Bradley, P., and Hogg, C. D.: Pneumococcic Meningitis in the Newborn, J. PEDIAT. **26**: 406, 1945.
22. Bradford, W. L., and Kelley, H. W.: Gonococcal Meningitis in a Newborn Infant, Am. J. Dis. Child. **46**: 543, 1933.
23. Smith, M. H. D., Wilson, P. E., and Hodes, H. L.: Treatment of Influenzal Meningitis, J. A. M. A. **130**: 331, 1946.
24. Dubos, R. J.: Bacterial and Mycotic Infections in Man, Philadelphia, 1952, J. B. Lippincott Co., p. 501.
25. McKay, R. J., Ingraham, F. D., and Matson, D. D.: Subdural Fluid Complicating Bacterial Meningitis, J. A. M. A. **152**: 387, 1953.
26. Ross, S.: Treatment of Pyogenic Meningitis in Infants and Children, Clin. Proc. Child. Hosp., Washington, D. C. **11**: 49, 1955.
27. Craig, W. S.: Meningitis in the Newborn, Arch. Dis. Child. **11**: 171, 1936.
28. Kagan, B. M., Hess, J. H., Miriam, B., and Lundeen, E.: Meningitis in Premature Infants, Pediatrics **4**: 479, 1949.

ILIAC VEIN OBSTRUCTION CAUSED BY RETROPERITONEAL ABSCESS IN NEWBORN INFANTS

Review of the Literature and Report of Two Cases

Edgar Grunwaldt, M.D.,* and Edward J. Tomsovic, Major, MC, USA

THIS report deals with two newborn infants who had iliac retroperitoneal abscess. Initial diagnoses of hemangiomas of the thigh and abdominal wall were entertained. After the presence of venous obstruction was established, the most likely etiology seemed to be malignant tumor. Surgical exploration revealed the true cause to be abscess formation in a locus uncommonly involved nowadays. Venous obstruction as a manifestation of retroperitoneal abscess has not been reported previously.

REVIEW OF THE LITERATURE

A review of the literature on iliac retroperitoneal abscess shows that this is a well-known entity, the first description of which is hard to ascribe. In Ziemssen's *Cyclopedia of the Practice of Medicine*[1] published in 1877, Senator has a chapter on acute psoitis, giving a typical description of this condition. Among his references are several prior to 1850 and one by Fordyce in 1784. Under the name of acute psoitis this condition was described by Mynter in 1881.[2] Acute iliac adenitis was the diagnosis in the cases described in two articles which appeared at the turn of the century,[3, 4] and in the third decade of the present century this was a well-known condition both here and abroad.[5-9] It has been described also as psoas abscess,[10] and several articles have appeared on the subject from South America,[11-14] a series of seventy-seven cases being published by Largos García[12] of Argentina. While most of the authors have commented on the paucity of the literature on this particular subject, over 150 cases have been described throughout the years, an excellent article being that of Neuhof and Arnheim[15] in 1944.

The most recent report of iliac adenitis was made by Carson and Hartmann[16] who, in 1946, reviewed their results of treatment with sulfonamide and penicillin. Gross and Ladd,[17] in the 1953 edition of their textbook, *Surgery of Infancy and Childhood*, described iliac adenitis and mentioned twenty patients. They did not break down the group except by age, so that nothing specific can be said about the cases. Zadek,[18] in 1950, described acute nontuberculous psoas abscess as a clinical entity which he believed to be different from iliac adenitis, in that his patients showed no infected iliac glands at operation and the abscess seemed to be localized to the body of the psoas muscle and within its sheath.

From the Department of Pediatrics, University of California School of Medicine, San Francisco, Calif., and Madigan Army Hospital, Tacoma, Wash.

*Present address: 920 Cass Street, Monterey, Calif.

Clinically, however, these cases are indistinguishable from iliac adenitis with abscess.

ANATOMICAL CONSIDERATIONS AND PATHOGENESIS

The floor of the iliac fossa is formed by the iliopsoas muscles which are covered by the thick iliac fascia attached laterally to the iliac crest and mesially to the brim of the true pelvis. The iliac and transversalis fasciae become continuous with each other at that segment of the inguinal ligament lateral to the external iliac vessels. In the region of the external iliac vessels they pass inferiorly beneath the inguinal ligament, the transversalis fascia in front of and the iliac fascia behind the vessels. In the retroperitoneal tissues of the iliac fossa are the ureter, the spermatic or ovarian vessels, the genitofemoral nerve, and the external iliac artery and vein. The external iliac lymph nodes form three chains around the external iliac vessels. These receive lymphatics from the inguinal nodes, the internal and external genitals, the umbilicus, the inferior abdominal wall, and the internal iliac nodes.

Acute iliac adenitis is the most common cause of iliac retroperitoneal abscess in children. The diagnosis of iliac adenitis is difficult to prove conclusively, and is possible only at surgery. Even then, in the presence of a large abscess, the lymph nodes may be broken down or not visualized, so that many cases are attributed to "cause unknown." Clinically, a number of these appear to result from iliac adenitis. Of the known causes, infection of the lower extremities is the most common,[12] and *Staphylococcus aureus* the most frequent causative organism. Other causes of iliac retroperitoneal abscess are ruptured appendix, intestinal lesions, such as diverticulitis, carcinomatosis, gynecological diseases, post-partum infections, genitourinary infections, and metastatic abscess following septicemia, most of these secondary to acute mastoiditis and otitis. Sixty per cent of cases of iliac adenitis occur in children.[13]

DIAGNOSIS AND CLINICAL COURSE

Common symptoms in this condition are lower abdominal or inguinal pain; pain in the hip, thigh, or knee; chills and fever; dysuria or urinary retention. These symptoms may persist from a few days to a number of months. The usual physical findings are tenderness in the inguinal or iliac regions, marked psoas spasm, the presence of a mass above Poupart's ligament, or palpation of a mass by rectum or vagina, and enlarged inguinal nodes.

The most constant laboratory finding is leukocytosis with a left shift. Roentgenograms may show blurring of the psoas shadows and lumbar scoliosis as the result of psoas spasm. Urograms may show displacement of the ureter and bladder, and hydronephrosis. This has been described by Coutts[14] and can be seen in some of the University of California cases discussed below (Table I). As will be seen in our two cases, many of these findings may be absent in the newborn infant.

Two common differential diagnoses in children are acute appendicitis and hip infections. Iliac adenitis differs from appendicitis in the presence of fever, marked psoas spasm, and the

absence of signs of peritoneal irritation. While iliac adenitis may result in limitation of hip extension, other motions of the hip will be normal. Roentgenograms will be negative. (Iliac adenitis following hip infection has been described.[16])

Formerly, treatment was delayed until an abscess could be detected by palpation, at which time extraperitoneal surgical drainage was instituted. In those cases where drainage was not performed, the abscess frequently ruptured into the vagina, rectum, or bladder, or pointed in the thigh. In some cases the abscess spread upward, perforated the diaphragm, and produced empyema, usually causing death. The over-all mortality rate was approximately 5 per cent. In the Largos García series[12] the abscess reabsorbed without treatment in one-fifth of the cases.

REVIEW OF CASES FROM UNIVERSITY OF CALIFORNIA HOSPITAL OVER THIRTY-EIGHT-YEAR PERIOD

A review of the University of California Hospital records from 1916 to 1954 revealed nineteen cases of iliac retroperitoneal abscess and one case clinically typical of acute iliac adenitis without suppuration (Table I). All had the classical signs and symptoms of this condition already described. Only the less frequent findings are mentioned in the table. Adults are included because some of them illustrate points to be brought out in our two cases. Most of these cases predate the use of antibiotics and chemotherapeutics. Five out of the six children in this group had infection in the lower extremities and all of them probably represent iliac adenitis with suppuration. In two of them this is further substantiated by the presence of draining inguinal nodes.

CASE REPORTS

CASE 1.—A 3-week-old white male was transferred to Madigan Army Hospital from Larson Air Force Base on Jan. 17, 1955, with a diagnosis of hemangioma of the right thigh. The infant was born at Larson Air Force Base Hospital on Dec. 23, 1954. There had been no pre- or postnatal difficulty. He was circumcised on the third day of life and discharged the following day. He did well until five days before entry into the hospital, at which time the right foot was first noticed to be swollen. The following evening the entire right lower extremity was cyanotic and the leg appeared to be swollen to twice its normal size. It was recalled that on the fifth day of life the baby had been noted to draw up the right lower extremity and cry when the extremity was pulled. This condition persisted and he was taken to Larson Air Force Base Outpatient Clinic on Jan. 13, 1955, and transferred from there to Madigan Army Hospital. From that date there was a marked increase in size of the right lower extremity. The leg became more cyanotic with crying, but there were no other signs or symptoms. There was no history of infection in the circumcision, the umbilicus, or on the lower extremities.

On physical examination the infant appeared healthy in all respects except for his right lower extremity, which was enlarged, cyanotic, and edematous, with a network of dilated venules over the anterior thigh. Circumference of the right thigh was nine inches, compared to seven inches for the left thigh. The right calf was five and three-quarter inches, the left calf four and one-half inches in circumference. The right lower extremity was held in abduction and flexion, and an attempt to extend it produced crying. An area of induration or a mass could be palpated in the upper portion of the thigh extending into the

TABLE I

AGE YR.	SEX	CAUSE	LESS FREQUENT FINDINGS	TREATMENT	OUTCOME
63	M	Osteomyelitis of hip	None	Surgical drainage	Recovered from abscess
62	M	Unknown	Displaced ureter and bladder	Surgical drainage	Recovered from abscess
61	M	Osteomyelitis of ileum	None	Surgical drainage	Recovered from abscess
58	M	Unknown	None	Surgical drainage	Recovered from abscess
56	M	Perforation, diverticulitis	None	Surgical drainage	Recovered from abscess
51	F	Carcinoma of cervix	Hydronephrosis and displaced bladder	Drained spontaneously per vagina	Recovered from abscess, hydronephrosis subsided
46	F	Carcinoma of cervix	Ureter displaced	Surgical drainage	Died, carcinoma
46	F	Carcinoma of cervix	Ureter displaced	Surgical drainage	Recovered from abscess
45	F	Perforation, bladder second fulguration	None	Surgical drainage	Died, tuberculous kidney and bladder
45	F	Pelvic inflammatory disease	Edema, legs	Surgical drainage	Recovered
39	F	Dilatation and curettage	None	Surgical drainage	Recovered
27	F	Perforation of appendix	Dilated veins left abdominal wall; edema, left leg—abscess on right	Drainage spont. over right trochanter	Died; autopsy: thrombosis both femoral and external iliac veins
21	M	Regional ileitis	Ureter stretched	Surgical drainage	Recovered from abscess
16	M	Perforation of appendix	None	Surgical drainage	Recovered
1	F	Cellulitis, leg	None	None; typical findings of iliac adenitis; no abscess	Recovered
1½	M	Infected laceration, knee	Inguinal abscess drained; edema, leg	Refused operation, broke into bladder and drained	Unknown
2	F	Infected burn, thigh	Ureter displaced; inguinal abscess drained	Sulfathiazole	Recovered
7	F	Ear infection	Extension to adductor	Surgical drainage	Recovered
12	M	Osteomyelitis of foot and spine	Abscess both sides, 1 mo. apart	Surgical drainage	Recovered from abscess
15	F	Osteomyelitis of hip	None	Surgical drainage	Recovered from abscess

right lower quadrant of the abdomen just beyond the inguinal ligament. Rectal examination was negative.

Laboratory studies the day following admission showed a white blood cell count of 15,000: 68 per cent neutrophils, 28 per cent lymphocytes, 3 monocytes, and one eosinophil. Hemoglobin was 14.2 grams, hematocrit 42,

Fig. 1.—Right saphenous venogram. Radiopaque material enters the femoral vein but further passage is obstructed at the level of the inguinal ligament. Collateral route through the pudendal vein is seen. Soft tissue swelling of the entire limb is evident. Case 1. (U. S. Army Photograph.)

and urinalysis was normal. Throat culture showed hemolytic *Staph. aureus* in large numbers.

Roentgenograms of the right lower extremity revealed no bony pathology. The muscle pattern of the right thigh was obliterated by soft tissue shadow. A right saphenous venogram was performed which showed occlusion of both the external iliac and the femoral veins (Fig. 1). An intravenous urogram was performed which showed indentation of the bladder on the right (Fig. 2). The impression of the roentgenologist was that a mass in the pelvis was causing venous obstruction.

By the fourth hospital day edema had progressed in the leg and had involved the scrotum and penis. On the fifth hospital day surgical consultation produced a tentative diagnosis of rapidly progressing hemangiosarcoma of the thigh. An operation for diagnosis and possible radical surgery was scheduled.

Surgery was performed the same day, at which time an abscess was found in the region of the femoral canal. This extended superiorly in the

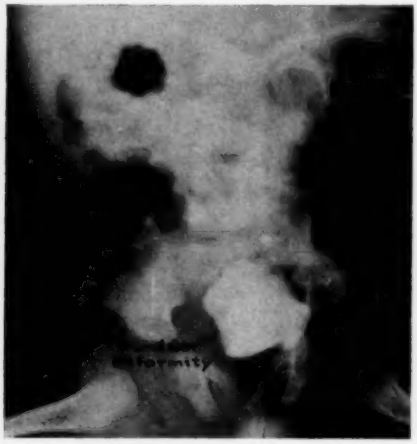


Fig. 2.—Intravenous urogram. A rounded indentation in the right wall of the bladder is demonstrated. Case 1. (U. S. Army Photograph.)

retroperitoneal space into the iliac fossa and inferiorly into the adductor space. The mechanism of this extension is discussed by Freiberg and Perlman.[19] Biopsy of an inguinal lymph node made at the time of the operation showed acute inflammation. Hemolytic *Staph. aureus* resistant to penicillin but sensitive to chloramphenicol, chlortetracycline, oxytetracycline, and erythromycin was cultured from the abscess.

Following surgery there was prompt improvement of leg color and diminu-

tion of edema. The infant's temperature before the operation was 37.4° and 37.8° C., with the highest recording at 38° C. Following surgery his temperature in the first hour was 38.8° C., after which it remained normal. Therapy with erythromycin was started. Improvement continued and the infant was discharged on the fourteenth hospital day. Symptoms had subsided entirely, but the wound had not completely closed and was draining slightly.

History revealed that when the infant was 6 days old, the mother had developed fever, fatigue, and generalized malaise, and had had a vaginal hemorrhage. She had been admitted to the University of California Hospital for treatment of endometritis and returned home when the baby was 11 days old. At this time she noted the baby to be fussy, which she attributed to inadequate intake of milk and accordingly started formula supplementation. However, he continued

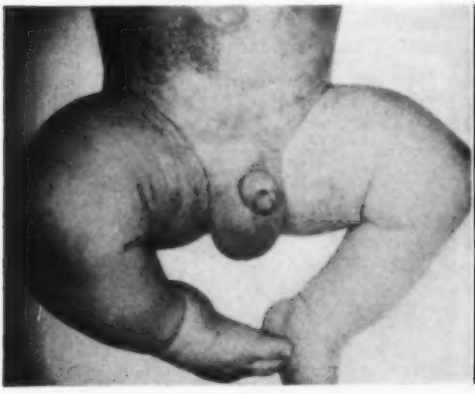


Fig. 3.

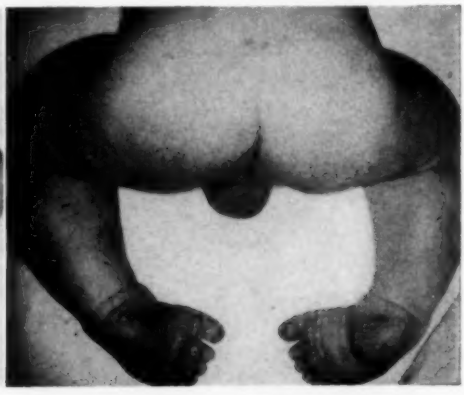


Fig. 4.

Fig. 3.—Preoperative photograph of the lower extremities showing collateral venous circulation, cyanosis, and edema. Case 2.
Fig. 4.—Same patient as shown in Fig. 3, posterior view.

Follow-up examination July 16, 1956, revealed a sturdy, healthy child with no limp or asymmetry. The inguinal scar was well healed. X-ray films revealed normal bony contours of hips and pelvis.

Case 2.—A white male infant was born at the University of California Hospital on Feb. 16, 1956, following an uneventful pregnancy and delivery. He was circumcised on February 19 and discharged the following day, at which time physical examination was negative. He was readmitted to the University of California Hospital at age 3 weeks because of irritability and cyanosis of both lower extremities.

to be irritable until admission to the hospital. Five days prior to hospital admission the mother noticed that both lower extremities became cyanotic when the baby cried, particularly when he was lying on his back. There was no history of infection of the umbilicus, circumcision, or extremities.

Aside from irritability, positive physical findings were limited to the lower abdomen, thighs, and buttocks, where there was a vast network of dilated venules. There was cyanosis of the lower extremities which became more marked with crying, and edema extending up to the groins. The right thigh measured seven inches, the left

thigh seven and one-half inches in circumference. There were large masses of matted inguinal nodes bilaterally (Figs. 3 and 4).

Initial laboratory work revealed a white blood cell count of 26,600, with 68 per cent neutrophils, 38 per cent lymphocytes, 10 per cent monocytes, 4 per cent eosinophils, and 4 per cent basophils. Hemoglobin was 14.2 grams, and urinalysis was within normal limits. Throat culture revealed

The dermatology and peripheral vascular disease consultants felt that this condition was produced by either a hemangioma or a venous obstruction from retroperitoneal malignancy. Because of the high white blood cell count, three blood cultures were drawn, all of which were negative. Repeated rectal examinations revealed no mass.

Plain films of the abdomen revealed a homogeneous pelvic mass displacing

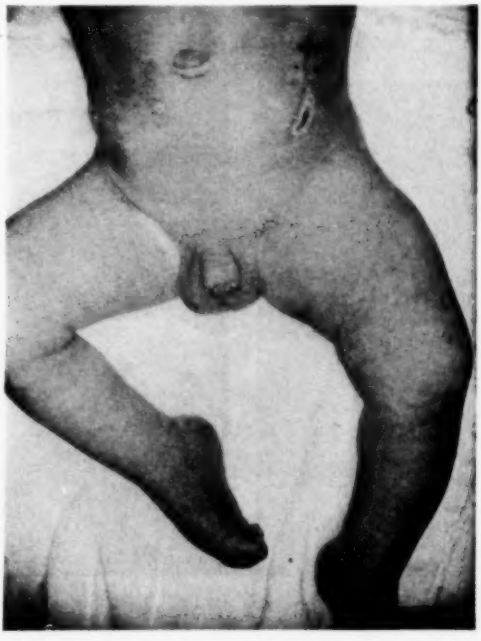


Fig. 5.—Photograph taken one week postoperatively, showing marked improvement of the lower extremities. Case 2.

Staph. aureus, Staphylococcus albus, alpha streptococcus and *Neisseria catarrhalis.*

The infant was afebrile throughout his hospital stay except for the fourth day, when his temperature was 38.4° C. He continued to eat well and to gain weight. White blood cell count increased to 38,900 with 75 per cent polymorphonuclear cells and 11 myeloblasts, and remained in this range until surgery.

the rectum and colon anteriorly and superiorly. Barium enema confirmed displacement of the sigmoid and descending colon anteriorly and to the right by a retroperitoneal mass. Intravenous pyelograms demonstrated anterior displacement of the ureters and bladder (Fig. 6). A left saphenous venogram showed obstruction of the external iliac veins with collateral circulation (Fig. 7).

One of us (E. G.) saw this infant on rounds and, from experience of the

case previously described, suggested the diagnosis of retroperitoneal abscess.

On the eighth hospital day a left lower quadrant mass became palpable just above Poupart's ligament. The upper margin of the mass was just below the level of the umbilicus. It was firm and nontender. The edema had progressed, involving the penis and scrotum. He was taken to surgery the same day.

The retroperitoneal space was explored on the left side, where a large abscess was found in the iliac fossa and drained. Culture of the pus was taken, drains were inserted, and therapy with penicillin and chloramphenicol was instituted. There followed a pronounced improvement in the appearance of the left thigh. However, a mass was now palpated in the right iliac fossa.

On the tenth hospital day another operation was performed; an abscess in the right iliac fossa extending into the upper part of the thigh was evacuated of approximately 100 c.c. of pus. Following surgery there was improvement of the right lower limb also (Fig. 5).

The white blood cell count on the day following this operation was 8,800, with 64 per cent neutrophils and 36 per cent lymphocytes. Culture of the pus from both abscesses revealed hemolytic *Staph. aureus* moderately sensitive to penicillin, chloramphenicol, and tetracycline, and quite sensitive to neomycin and several combinations of the above drugs. Recovery was uneventful except for a foot drop on the right side due to peroneal palsy.

Fig. 6.—Intravenous pyelogram showing displacement of the ureter and bladder anteriorly by retroperitoneal mass. Case 2.

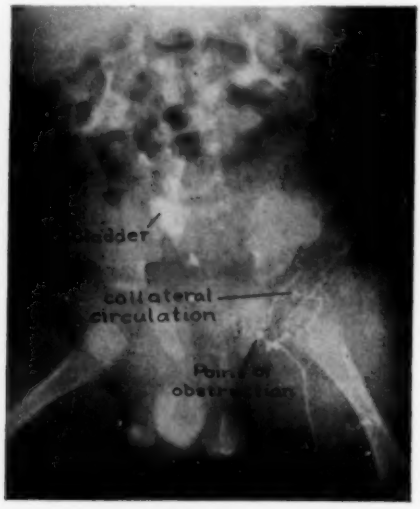


Fig. 7.—Saphenous venogram and simultaneous intravenous pyelogram showing obstruction at inguinal ligament, extensive collateral circulation, and compression of the bladder by the left abscess. Case 2.

The baby was last seen on May 29, 1956, at which time he appeared quite healthy. Both surgical scars were well healed and the foot drop was somewhat improved.

DISCUSSION

Anatomically, these two cases are typical of iliac retroperitoneal abscess, as proved by surgery. The lack of classical abscess symptoms is consistent with the age of the patients. Both

cases are probably secondary to iliac adenitis, because of the frequency of this condition in children and the presence of enlarged inguinal glands. The prominent signs of venous obstruction are considered related to the small capacity of the iliac fossae and the compressibility of the veins therein, rather than to mere massiveness of the abscesses. There are a number of cases in the literature with symptoms of many months' duration, with large collections of pus, yet without evidence of venous obstruction other than edema[14] (Table I).

No cases of retroperitoneal abscess in very young infants have been reported previously, 7 months being the youngest age in the literature. Perhaps this would explain the fact that the picture of iliac venous obstruction has not been described before.

Although these two cases might have to be classified as due to "cause unknown," we cannot help wondering why, in the preantibiotic era when several hundred cases had been described, none was reported in the newborn infant. In both of our cases we feel that the portal of entry was likely the circumcision site, because of (a) the enlarged inguinal nodes (lymphatic drainage of the penis is primarily through these nodes); (b) bilaterality of abscess formation in Case 2 (this suggests a midline portal of entry); (c) the onset of symptoms in the first two weeks of life; (d) the absence of signs pointing to another portal of entry.

The large number of elective circumcisions now being performed on newborn infants and the increasing incidence of staphylococcal infections recently noted may account for the occurrence of these two cases at the present time. There is no way of proving this theory unless further cases of the condition described are reported to occur primarily in circumcised males.

The role of the roentgenogram in localizing the pathologic process is noteworthy. No other clinical diagnostic tool proved so helpful. However, it remains for surgery to disclose the true nature of the obstructive mass and early intervention is advocated.

SUMMARY

Two cases of iliac vein obstruction due to iliac retroperitoneal abscess are reported. This condition as a presenting sign of retroperitoneal abscess has not been reported in the literature to date.

The literature is reviewed and common signs and symptoms of this condition are described.

The argument for circumcision site as the portal of entry of the infection is presented.

REFERENCES

1. Ziemssen, H. W. von: Cyclopedia of the Practice of Medicine (Albert Buck, editor American ed.), vol. 16, New York, 1877, W. Wood & Company, pp. 96-99.
2. Mynter, H.: Acute Psoitis, Buffalo M. & S. J. **21**: 202, 1881-1882.
3. Pegram, J. C., Jr.: Report of Two Cases of Suppuration of Retromesenteric Lymph Nodes, Tr. Rhode Island M. Soc. **6**: 643, 1903-1904.
4. Hamann, C. A., Jr.: Suppuration in the Retroperitoneal Glands, Cleveland M. J. **6**: 399, 1907.
5. Bailey, H.: Suppurating Deep Iliac Glands, Practitioner **124**: 223, 1930.
6. Hyman, A.: Suppurative Retroperitoneal Pelvic Lymphadenitis, Ann. Surg. **91**: 718, 1930.
7. Ingelrans, P., and Minne, J.: Onze observations psoitis primitives chez des enfants et des adolescents, Bull. et mém. Soc. nat. de chir. **58**: 349, 1932.
8. Neuhof, H.: Retroperitoneal Abscess With Obscure Clinical Manifestations, J. Mt. Sinai Hosp. **4**: 843, 1938.
9. Irwin, F. G.: Acute Iliac Adenitis. Report of 18 Cases, Arch. Surg. **36**: 561, 1938.

10. Rogers, M. H.: Psoas Abscess From Lumbar Retroperitoneal Lymph Glands, Am. J. Orth. Surg. **9**: 232, 1911-1912.
11. Del Campo, R. M., and Barberousse, C. M.: Las adenitis iliacas agudas en el niño, Arch. pediat. Uruguay **4**: 43, 1933.
12. Largos García, A.: La adenitis ilíaca aguda, Semana méd. **38**: 1160, 1931.
13. Lugones, C.: Adenitis aguda de los ganglios ilíacos, Rev. méd. lat. amer. **11**: 719, 1926.
14. Coutts, W. E.: Acute Inflammation of Deep Iliac Lymph Nodes, Ann. Surg. **86**: 782, 1927.
15. Neuhof, H., and Arnheim, E. E.: Acute Retroperitoneal Abscess and Phlegmon: Study of 65 Cases, Ann. Surg. **119**: 741, 1944.
16. Carson, M. J., and Hartmann, A. F.: Diagnosis and Management of Severe Infections in Infants and Children. A Review of Experience Since the Introduction of Sulfonamide Therapy. VI. Acute Iliac Lymphadenitis, J. PEDIAT. **29**: 183, 1946.
17. Gross, R. E., and Ladd, W. E.: The Surgery of Infancy and Childhood, Philadelphia, 1953, W. B. Saunders Co., p. 392.
18. Zadek, I.: Acute Non-Tuberculous Psoas Abscess. A Clinical Entity. Report of Seven Cases, J. Bone & Joint Surg. **32-A**: 433, 1950.
19. Freiberg, J. A., and Perlman, R.: Pelvic Abscesses Associated With Acute Purulent Infection of Hip Joint, J. Bone & Joint Surg. **18**: 417, 1936.

Some Early Record Breakers

We are certainly inform'd by an Eye Witness, That there is at *New-Haven* in *Connecticut*, a Child named *Enoch Turner*, who when he was Born weighed 11 Pounds, & when he was 18 months old (which was on the second of this month) weighed 46 Pounds & an half; He was 3 Feet & 2 Inches high; on the naked Body over the Breast 2 Foot round; 10 Inches round just above his Knee, 9 round the Calf of his Leg, 6 & a quarter round the small of his Leg, 7 round his Arm just above his Elbow, 5 round his Wrist; (these Dimensions being taken from his Father's Mouth.) and his strength is in proportion to his bigness, for he can carry a Pail of Water almost full. He has about the Pudenda symptoms of Ripeness equal to a Lad of 16 years old, and his Voice is like that of a Man grown.

FROM THE BOSTON GAZETTE, May 29, 1738

Lately died at Windsor, (State of Vermont) Esther Dean, aged 2 years and 20 days, daughter of Mr. Willard Dean of that town, the extraordinary grossness of this child, it is supposed was the occasion of her death. . . . . She weighed before a year old, upwards of 70 lb. She is the third child Mr. Dean has lost of such extraordinary bulk, and all at about the same age.

FROM NEW HAMPSHIRE GAZETTE AND GENERAL ADVERTISER, Feb. 25, 1785

Died Polly Proctor, daughter of John Jr., quinsey. A remarkably large child, weighed between seventy and eighty weight. Two years, seven months. October 24, 1793.

FROM IPSWICH VITAL RECORDS (DEATHS)

EXPLOSION OF NURSING BOTTLES

PRESTON J. BURNHAM, M.D.
SALT LAKE CITY, UTAH

STATISTICS show that the greater number of all injuries occur in the home. There we are exposed to numerous utensils, electrically powered apparatus, gas-controlled equipment, rugs on slippery floors, and even steam which develops terrific pressure when it is not permitted to expand.

Oftentimes, however, we are all guilty of ignoring these and other common manifestations of nature's laws in our homes and offices. Perhaps long familiarity leads to forgetfulness of these dangers in our surroundings. It is only when we sustain actual injury from the mishandling of potentially injurious equipment or recognize their subtle dangers from the vicarious appreciation of the injuries of others that we resume caution. This brief case report is presented only to restimulate this awareness of danger.

CASE REPORT

On July 28, 1956, Mrs. E. J. was performing a routine sterilization of drinking water for her infant. The sterilizer was a standard electric type with hinged cover, and held eight nursing bottles. The plastic bottle covers with nipples inverted had been screwed on snugly.

From the Department of Surgery, College of Medicine, The University of Utah, and St. Mark's Hospital.

After an undetermined length of time of boiling, possibly one-half hour, the patient opened the lid of the sterilizer. As rapidly as she could note that the sterilizer water had boiled dry, six of the eight bottles exploded like hand grenades, driving countless glass particles into her face and neck (Fig. 1). Those in the neck penetrated nearly one and one-half inches, while some over the mandible and zygoma penetrated to the bone. The aluminum shield on the ceiling over the stove was perforated by nearly as many particles.

Fig. 1.

Perhaps publication of this incident will avoid recurrences.

THE RESPONSIBILITIES OF THE MEDICAL PROFESSION IN THE USE OF X-RAYS AND OTHER IONIZING RADIATION

Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation

1. The United Nations General Assembly, being aware of the problems in public health that are created by the development of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radiotherapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

2. Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation, diagnosis, and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

3. It is now accepted that the irradiation of human beings, and particularly of their germinal tissues, has certain undesirable effects. While many of the somatic effects of radiation may be reversible, germinal irradiation normally has an irreversible and therefore cumulative effect. Any irradiation of the germinal tissues, however slight, thus involves genetic damage which may be small but is nevertheless real. For somatic effects there may, however, be thresholds for any irreversible effects, although if so these thresholds may well be low.

4. The information so far available indicates that the human race is subjected to natural radiation,* as well as to artificial radiation due to its medical applications, to atomic industry and its effluents and to the radioactive fall-out from nuclear explosions. The Committee is aware of the potential hazards that such radiation involves, and it is collecting and examining information on these subjects.

*The radiation due to natural sources has been estimated to cause between 70 and 170 millirem of irradiation to the gonads per annum in most parts of certain countries in which it has been studied, although higher values are found locally in some areas. See the reports "The hazards to man of nuclear and allied radiations" published by the United Kingdom Medical Research Council in June, 1956, in which also the millirem is defined; and from information submitted to the Committee.

5. The amount of radiation received by the population for medical purposes is now, in certain countries, the main source of artificial radiation and is probably about equal to that from all natural sources. Moreover, since it is given on medical advice, the medical profession exercises responsibility in its use.

6. The Committee appreciates fully the importance and value of the correct medical use of radiation, both in the diagnosis of a large number of conditions, in the treatment of many such diseases as cancer, in the early mass detection of conditions such as pulmonary tuberculosis, and in the extension of medical knowledge.

7. Moreover, it appreciates fully the contribution of the radiological profession, through the International Commission on Radiological Protection* in recommending maximum permissible levels of irradiation. As regards those whose occupation exposes them to radiation, the establishment of those levels depends on the view that there are doses which, according to present knowledge, do not cause any appreciable body injury in the irradiated individual; and also on the consideration that the number of people concerned is sufficiently small for the genetic repercussions upon the population as a whole to be slight. Whenever exposure of the whole population is involved, however, it is considered prudent to limit the dose of radiation received by germinal tissue from all artificial sources to an amount of the order of that received from the natural background radiation.

8. It appears most important therefore that medical irradiations of any form should be restricted to those which are of value and importance, either in investigation or in treatment, so that the irradiation of the population may be minimized without any impairment of the efficient medical use of radiation.

9. The Committee is consequently anxious to receive information through appropriate governmental channels as to the methods and the extent by which such economy in the medical use of radiation can be achieved, both by avoiding examinations which are not clearly indicated and by decreasing the exposure to radiation during examinations, particularly if the gonads, or the fetus during pregnancy, lie in the direct beam of radiation. It seeks, in particular, to obtain information as to the reduction in radiation of the population which might be achieved by improvements in instrument design by fuller training of personnel, by local shielding of the gonads, by choosing appropriately between radiography and fluoroscopy, and by better administrative arrangements to avoid any necessary repetition of identical examinations.

10. The Committee also seeks the cooperation of the medical profession to make possible an estimate of the total radiation received by the germinal tissue of the population before and during the child-bearing age. It considers it to be essential that standardized methods of measurement, of types at present available, should be widely used to obtain this information and it

*See the report of the International Commission on Radiological Protection (published in the *British Journal of Radiology*, suppl. 6, December, 1954; in the *Journal français d'electro-radiologie*, No. 10, October, 1955, etc., and revised in 1956).

emphasizes the value of adequate records, maintained by those using radiation medically, by the dental profession, and by the responsible organizations in allowing such radiation exposure to be evaluated. The Committee is convinced that information of this type will make it possible to decrease the total medical irradiation of the population while preserving and increasing the true value of the medical uses of radiation.

Measles in the Year 1670

The measles set in early as usual; i.e., at the beginning of January. They gained strength every day, until they reached their height, about the vernal equinox. After this they gradually decreased at the same rate; and by the month of July were wholly gone. As far as I have hitherto seen, I believe these measles to be the most perfect disease of their genus, for which reason I shall record their history with all the care and minuteness that the observations which I then made will warrant.

This disease begins and ends within the above-named period. It generally attacks infants, and, with them, runs through the whole family. It begins with shiverings and shakings, and with an inequality of heat and cold, which, during the first day, mutually succeed each other. By the second day, this has terminated in a genuine fever, accompanied with general disorder, thirst, want of appetite, white (but not dry) tongue, slight cough, heaviness of the head and eyes, and continued drowsiness. Generally there is a weeping from the eyes and nostrils; and this epiphora passes for one of the surest signs of the accession of the complaint. But to this may be added another sign equally sure; viz. the character of the eruption. Although measles usually shows itself by an exanthema upon the face, there appears upon the breast a second sort of breaking-out. This consists in broad red patches on a level with the skin, rather than true exanthemata. The patient sneezes as if from cold, his eyelids (a little before the eruption) become puffy; sometimes he vomits: oftener he has a looseness; the stools being greenish. This last symptom is commonest with infants teething, who also are more cross than usual. The symptoms increase until the fourth day. At that period (although sometimes a day later) little red spots, just like flea-bites, begin to come out on the forehead and the rest of the face. These increase both in size and number, group themselves in clusters, and mark the face with largish red spots of different figures. These red spots are formed by small red papulae, thick set, and just raised above the level of the skin. The fact that they really protrude, can scarcely be determined by the eye. It can, however, be ascertained by feeling the surface with the fingers. From the face—where they first appear—these spots spread downwards to the breast and belly; afterwards to the thighs and legs. Upon all these parts, however, they appear as red marks only. There is no sensible protuberance by which they show themselves above the level of the skin.

THOMAS SYDENHAM

Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS white female, aged 8 years 5 months, was first admitted to The Children's Medical Center at the age of 5 years 2 months with a history of having had an upper respiratory infection seven days previously. This had been treated with a sulfonamide for three days. Over the period from the onset of the respiratory infection until hospitalization, she developed edema, anuria, and hypertension. Urine samples obtained in the first two days of hospitalization had an acid reaction, specific gravities of 1.046 and 1.050, and a four plus albumin. The urine sediment contained 3 to 4 erythrocytes, 8 to 10 leukocytes, and 10 to 15 granular casts and occasional hyaline casts per high-power field. The urine contained no sulfonamide crystals. The sulfonamide blood level was 0. The antistreptolysin titer was 51 units. The serum nonprotein nitrogen was 80 mg. per cent and the potassium 7.3 meq. per liter.

The patient was given intravenous fluids calculated to cover her urine output and insensible water loss. Over the three-week period of her hospitalization the hypertension, azotemia, and hyperkalemia disappeared but the edema and albuminuria continued. The total serum protein was 3.6 gram per cent and total cholesterol 900 mg. per cent. Near the middle of her hospital stay one positive urine culture was obtained for *Pseudomonas aerogenosa*, but subsequent cultures were negative; no specific therapy was given for this. A ten-day course of cortisone, 300 mg. per day, was given, with a resulting diuresis and a loss of 15 pounds in weight. At the time of discharge, the urine examination showed a pH of 7.5, specific gravity 1.016, albumin 0, erythrocytes 0, leukocytes 3 to 6 per high-power field, and rare granular casts.

At 5 years 7 months, the patient was readmitted with a reaccumulation of the edema. Because of the discovery of a urinary tract infection with *Bacillus proteus*, no steroid therapy was given. Various antibiotics were administered in an attempt to eradicate the urinary infection, without success, during a five-week period of hospitalization.

A third admission occurred one week after the previous discharge because of respiratory distress secondary to ascites; this was relieved by a paracentesis. The urine pH was now 6.5, the specific gravity varied from 1.007 to

1.034 and it contained albumin, 3 plus, many white cells, and granular casts but no erythrocytes. Three of four urine cultures contained *B. proteus*. The serum protein level was again low and a serum calcium level was 5.9 mg. per cent. The urinary infection was treated with Chloromycetin and streptomycin, without benefit, over a three-week period of hospitalization.

A fourth admission was required one month subsequent to the previous discharge because of the reaccumulation of abdominal fluid. On this admission the blood pressure was recorded as 130 mm. Hg systolic and 84 diastolic. The urine remained as on the previous admission and the serum nonprotein nitrogen now was 69 mg. per cent. The urinary tract infection continued unabated despite antibiotics. A roentgenological estimation of bone age showed a maturation arrest of two years below the chronological age of 6 years.

Over the next two years the edema fluctuated and then gradually disappeared, so that in the final year of life she was virtually free of edema. An anemia sufficient to require repeated transfusions was constantly present. The serum nonprotein nitrogen had gradually risen. Eleven days prior to death she developed spontaneous nasal and rectal bleeding, and two days later became progressively lethargic and dyspneic. These symptoms were accompanied by vomiting.

At the time of the final hospital admission, seven days before death, physical examination revealed the patient to be desperately ill and comatose, with a temperature of 99° F., pulse 120 per minute, respirations 35 per minute, and blood pressure 120 mm. Hg systolic and 80 diastolic. The skin was dry and there was dried blood about the nares and the rectum. The heart was slightly enlarged and there was an apical presystolic gallop. Slight ankle edema was present.

The laboratory examination at the time of admission revealed a pH of 5.5, specific gravity 1.009, albumin 2 plus, acetone 1 plus, with a sediment containing 1 to 3 erythrocytes, 15 to 20 leukocytes, and an occasional granular cast per high-power field. The blood hemoglobin was 9.5 gram per cent, and the peripheral leukocyte count, 38,000 per cubic millimeter, with a moderate shift to the left in the granulocytes on the smear. The serum chemistries were as follows: nonprotein nitrogen, 170.8 mg. per cent; pH, 7.02; carbon dioxide content, 4.2; sodium, 136; potassium, 6.2; and chlorides 97 meq. per liter. The calcium was 5.5 and the phosphorus 18.4 mg. per cent. A blood culture and a urine culture were sterile. In spite of oxygen therapy, digitalization, antibiotics, glucose and lactate by vein, Amphojel and calcium by mouth, and sedatives, she failed to improve, began to convulse, and died.

DISCUSSION

DR. DAVID GITLIN.*—At the time of the first admission, aside from the anuria, this patient had a picture which was consistent with lipoid nephrosis. She had oliguria, generalized edema, a 4 plus urinary albumin, a serum protein three days after admission which was reported as 3.5 gram per cent, and a serum cholesterol of 900 mg. per cent. There are several features of her illness which do not fit the classical description of nephrosis.

*Dr. David Gitlin is Associate Physician, The Children's Medical Center, and Associate in Pediatrics, Harvard Medical School.

These are the hypertension, anuria, a nonprotein nitrogen of 80 mg. per cent, and a serum potassium of 7.3 meq. per liter. It is stated, however, that she had had an upper respiratory infection and was given a sulfa pill three times a day for three days. The sulfa administration was far less than that which is ordinarily used for therapy of an infection, but it does not take very much sulfa to induce a hypersensitivity reaction.

Did she have an acute glomerulonephritis at this time, which rapidly deteriorated into the nephrotic syndrome? Did she have renal disease prior to the onset of this episode for which she was admitted? Sulfa, we recognize, can cause three major intrarenal disturbances. One is an obstructive nephrosis, partly due to crystalline deposits, the second is a toxic nephrosis, and the third is an interstitial nephritis on a hypersensitivity basis. There were no crystals in the urine, which effectively eliminates the first of these. The course was not that of toxic nephrosis. Whether or not she had acute glomerulonephritis is the next point, and that is going to be the most difficult to determine. I do not think that the antistreptolysin titer helps very much.

I think it would be interesting at this point to try to find out how much albumin or protein she had to lose to get a serum protein level of 3.5 gram per cent. This may give us a clue as to the previously existing renal disease. The amount turns out to be a little on the phenomenal side. In the total body pool of albumin, there is approximately twice the amount of albumin in the circulation: in other words, if the patient had a plasma volume of 1,200 c.c., the volume of distribution of the albumin would be 2,400 c.c. At the onset of this illness, the patient would have had a normal serum albumin of about 4 grams per 100 ml. This would have given her a total body pool of about 96 grams of albumin, or if she had 6.5 grams total serum protein, this would have given her a total body pool of 156 grams of serum protein. About 75 to 95 per cent of the excreted urinary protein in nephrosis is albumin. Since the serum albumin in the edematous state in nephrosis is usually less than 1 gram per cent, her serum albumin suffered a fall of at least 2.5 grams per cent. If we then multiply the volume of distribution, 2,400 c.c., by this loss, to find out how much albumin she lost in this period of time, it turns out to be about 60 grams of albumin, or about 60 per cent of the total body pool. Now, remember, she had anuria; she also had oliguria after the anuria, yet she lost 60 grams of albumin—and how did she lose it? If one calculated the loss to be via the urine alone over this period of time, it turns out that she would have had a urinary concentration of albumin well over 10 grams per cent. This is clearly impossible. Well, then, where did she lose the albumin? Either she lost it through an increased rate of destruction during her present illness, or she had the disease prior to the onset of the first bout of edema, or both. In other words, at her first admission she may have had active all the mechanisms for the production of the nephrotic syndrome. I think this patient had lipoid nephrosis long before we observed the fact that she had edema. It was probably the superimposed upper respiratory infection that threw her into acute renal failure and

brought her to the hospital with generalized edema, anuria, hypertension, hyperkalemia, and azotemia.

At her second admission, whatever processes were operative when she was admitted the first time were still active.

On her third admission, the serum calcium was 5.9 mg. per cent. The serum calcium in nephrosis tends to be a bit on the low side, yet the very low level of calcium that one finds in these patients is still high enough to provide a sufficient amount of ionized calcium to prevent tetany, presumably because of the small amount that is protein bound.

On the fourth admission she apparently still had pyelonephritis.

The edema had at first fluctuated and then had been absent for the year prior to her final admission. If the kidney no longer excreted protein, it was because of one of two reasons—either glomerular permeability had improved, in the sense that the permeability to protein was now less than it was before, or that the glomeruli were so badly damaged that very little blood was flowing through them. If this were so, many of these glomeruli were now hyalinized or avascular. The anemia was still present and the nonprotein nitrogen was rising. These observations were well in accord with the feeling that glomeruli were now severely damaged. Whether this advancing renal impairment was due to the underlying nephrosis or to pyelonephritis, it is difficult to say. I think it would probably have been due to a combination of both. As I mentioned, the continuing anemia was also a bad prognostic sign, and I believe this has been well substantiated recently by careful studies done by Dr. Meteoff. Whether or not we will find signs of renal rickets in this particular patient, I do not know, but certainly the mechanism for it existed with the high phosphorus and low serum calcium levels.

Her last admission, I think, was very characteristic of uremia. All of the physical signs, blood studies, and serum chemistries were compatible with severe renal failure. The bleeding from the nose and rectum was also compatible with uremia; ulcers might be found anywhere in the nose and mouth or in the gastrointestinal tract. I think that the pathological findings will include a chronic glomerulonephritis with a superimposed chronic or healed pyelonephritis. I certainly think the pyelonephritis contributed to the demise of the individual. Even though it may have burned itself out, it might have contributed, in this instance, to the pathological alterations leading to renal failure. There are those who believe that the involvement of pyelonephritis in such an instance is more than coincidental.

There are a great many possible etiologies for the nephrotic syndrome and among these are drugs and poisons, in which case sulfonamide would be one of them; but these drugs usually result in lower nephron nephrosis, and the course is quite different from that which we see here. Nephrotic syndrome may be found in the course of amyloid disease but she had had no history of disease of organs other than the kidney. Diabetic renal disease might be considered, but there was certainly no evidence for it here. I assume a Wassermann was taken, and that there is no evidence for the diagnosis of syphilis. The patient might have had thrombosis of the renal veins —although I do not think so since she

would have had much more blood in the urine and her course would have been considerably different.

Then, let us consider the group of diseases, including subacute and chronic glomerulonephritis. There was one determination that could have helped us a great deal, which was not done on this particular patient. When she first came to the hospital with a generalized edema, if edema fluid had been taken and a total protein had been estimated on the edema fluid, we would have been able to determine whether or not she had acute glomerulonephritis. In acute glomerulonephritis, the edema fluid that is found is relatively high in albumin, ranging from 0.5 to 0.8 gram per cent, but much below the normal value of 1.5 to 2 grams per cent for interstitial fluid. It is in the range that one usually finds in patients with cardiac failure, and presumably the nephritic type of edema is due to a manifestation of cardiac failure or backward failure. Nephrotic edema, on the other hand, is due entirely to a decrease in the oncotic pressure of the plasma proteins, resulting in tremendous outpouring of water from the capillaries with practically no accompanying albumin. Thus the concentration of serum proteins in edema fluid is extremely low, around 5 mg. per cent, and far below the level in acute nephritis. That one determination could have helped us a great deal as to the etiology of the first episode.

We still have to explain this tremendous loss of protein, and therein, I think, lies the crux of the problem. What was actually happening in this particular patient? We did a series of determinations in other children with nephrosis or the nephrotic syndrome.[1] Normally, renal glomerular capillaries retain, within the lumen, about 99 per cent of the albumin flowing through. In nephrosis we find that protein retention has dropped down to about 94 per cent, 6 per cent being lost through the glomerular walls and excreted. This would seem to be a very small amount. The volume of filtrate is tremendous and although it may contain very small amounts of protein, one finds that the patient is actually excreting as much as 30 grams of albumin per day at the beginning of the disease. In a well-established disease, the patient may excrete only about 0.5 gram per day due to the fact that the serum protein concentrations are now very low. They may lose 90 per cent of their albumin. The question arises as to whether the albumin that is excreted is normal or abnormal, whether the glomerulus is at fault, or whether the tubules have failed to reabsorb protein. The albumin that passes through the glomerulus, so far as we can find out, is perfectly normal. It is indistinguishable by any of the tests we have available, even immunochemically, from normal serum albumin. Then, is it because the tubules have failed to reabsorb this small amount of protein, or is it because the increase in the permeability in the glomerulus is a real one? It would seem that the latter was true. There is an increase in the permeability of the glomerulus over that which the tubule can handle. If we calculate the amount of albumin passing out through the renal tubule, in the normal and in the nephrotic, we find that the nephrotic filtrate carries about ten times as much protein as does the normal. We do know that the normal tubule can reabsorb a certain amount

of protein. We find that the amount contributed to the filtrate by the damaged renal glomerulus is well above that which the tubule could normally reabsorb. So, one primary defect is not a failure in tubular reabsorption but rather an increase in the glomerular permeability. When you give a nephrotic patient albumin, it rapidly disappears from the circulation. About 25 to 50 per cent of this administered albumin appears in the urine. What has happened to the rest of it? It would appear that nephrotic patients with frank anasarca and edema have serum protein (especially albumin) turnover rates more than ten times the normal.[1] Yet, the protein synthesis rate in the nephrotic syndrome is normal for albumin, gamma globulin, and iron-binding globulin. We found that the amount of serum protein that these nephrotic children excrete, referable to the amount of serum protein they synthesize, may vary considerably. A patient with ascites and anasarca, for example, may excrete only 10 per cent of the protein that he synthesizes, and yet he has ascites and anasarca. Another patient, who may not have edema, may excrete 75 per cent of this amount. We were able to find at least two defects in the metabolism of serum proteins in the nephrotic syndrome. The first—renal loss of proteins due to increased glomerular permeability—is obvious. The second difficulty is an increase in the catabolism of plasma protein, and, particularly, albumin. One patient with mild proteinuria but no edema or ascites may have a perfectly normal catabolism of albumin and perfectly normal protein synthesis. He does not get into trouble, although he may be excreting 10 per cent of his synthesized albumin. Another patient with intermittent edema may have either a tremendous increase in his catabolism of albumin with mild proteinuria, or a tremendous increase in proteinuria with relatively normal catabolism of albumin. The patient with the full-blown nephrotic syndrome has both a severe proteinuria and a tremendous increase in albumin catabolism. When he recovers, either defect may disappear first. I think that this particular patient had the nephrotic syndrome before she was ever seen here, though this disease may not have been overt.

Just to recapitulate briefly, I believe this patient had the nephrotic syndrome with a superimposed chronic pyelonephritis.

DR. JACK METCOFF.—Instances of a nephrotic syndrome in which acute renal failure is ushered in by an upper respiratory infection within the first weeks or months of the disease are most unusual. One of the striking features of acute renal insufficiency in a child with acute glomerulonephritis is the development of a nephrotic syndrome within a month or one and one-half months after the acute renal insufficiency has cleared; subsequently, often the whole course of chronic glomerulonephritis in such a patient is shortened to a period of one and one-half to three years. In the adult the sequence of nephritis, either acute or subacute, followed by the nephrotic syndrome and then chronic glomerulonephritis and renal failure, has a course of many years. It is my impression that this child started with "acute renal failure."

The appearance of the patient's anuria, following the onset of her illness, had an extremely short latent

interval of five or six days. In acute glomerulonephritis the latent interval following infection is ten days. When this patient came to the hospital, we debated whether there might not have been an element of sulfonamide sensitivity in the etiology of the patient's renal difficulties.

Because she had the signs of a nephrotic syndrome, she was treated with cortisone. I believe now that cortisone therapy would be contraindicated in this patient at this particular time because we know that while it might conceivably produce a diuresis, it also might do considerable harm in producing a further marked decrease in blood flow through the kidneys by secondary obliteration of small vessels and, possibly, by producing considerable ischemic necrosis. This child, then, when she came in the next time, after having had a diuresis, did have a nephrotic syndrome. Her nephrotic syndrome was entirely different in its origin, we believe, than the nephrotic syndrome of most other children. If one were able to have a kidney biopsy at a comparable period of time in a child with typical nephrotic syndrome, one very well might have found just the usual lesion which is, namely, marked thickening of the glomerular membrane, some swelling of the tube cells, and a little change in the orientation of the phospholipids of the tubule cells. In this child I believe we would have found a striking degree of glomerular obliteration with considerable glomerular ischemia and an interstitial inflammatory reaction. Subsequently, she then went on to have complete obliteration of nephrons and I believe that, pathologically, one will find a kidney which contains little normal renal tissue. These glomeruli ought not to be only hyalinized, but completely fibrosed—with some evidence of an interstitial inflammatory response and with tubular casts secondary to pyelonephritis.

The subsidence of the edema by itself is not necessarily an unfavorable sign of the patient with the nephrotic syndrome, since this is the desired goal. It is a very bad sign, as Dr. Gitlin pointed out, if it is associated with failure of growth, which this child manifested strikingly: failure of bone maturation, increasing azotemia, electrolyte disturbances, and anemia. All of these occurred together here. This simply means progressive, severe, irreversible renal disease from which this child died.

DR. CRAIG.—Dr. Metcoff, I would like to know about your experiences with clinically demonstrable pyelonephritis in the presence of glomerulonephritis in children. How frequent a finding is that?

DR. METCOFF.—Pyelonephritis is a serious complication in the nephrotic syndrome and interferes with therapy. I agree with Dr. Gitlin in that I have no idea whether it occurs more frequently in them than it does in the normal population.

DR. CRAIG.—Would you like to predict the size of the kidneys? Her kidneys should weigh 74 grams apiece.

DR. METCOFF.—I would guess that her kidneys each weighed 25 grams.

DR. CRAIG.—Dr. Gitlin, would you like to predict the same?

DR. GITLIN.—I would not care to give a number value. She probably had very little renal tissue left.

DR. ALEXANDER NADAS.—I would like to say one thing. This theory that Dr. Gitlin mentioned—that the edema of acute glomerulonephritis is one of cardiac failure—was proposed by the late Dr. J. P. Peters a few years back.[2] I think it is very interesting and instructive, but I am not quite sure that I am ready to accept it because the people who go into congestive heart failure in the first bout of acute glomerulonephritis are not the patients who, by and large, are the most edematous. I wish I could persuade Dr. Gitlin to study it with us because it is an awfully interesting problem.

The other thing I would like to know is why patients with the nephrotic syndromes have large hearts. I have no good explanation for it, yet I know it is a pathological fact. The hypertension that is mentioned here in the fourth admission, 130/84, is certainly not significantly elevated to explain the cardiac enlargement. The patient, at this point, was not edematous, so that it cannot be ascribed to an increase in the extracellular fluid.

DR. METCOFF.—Dr. John Coffey and Dr. Conrad Riley in New York, and I think Dr. Neuhauser, all feel as I do—that, in general, patients with an uncomplicated nephrotic syndrome, not in renal failure, have rather small hearts by x-ray, and their hearts do not enlarge unless they die with a very severe, chronic renal disease.

DR. CRAIG.—The plasma volume in the nephrotic patient tends to be increased, does it not?

DR. METCOFF.—There is a difference of opinion about plasma volume measurements in the nephrotic syndrome. Dr. Eder and associates[3] believe that in patients who have a typical nephrotic syndrome, plasma volume is diminished during the acute phase, and that diuresis is associated with an increase in the plasma volume. This is despite the fact that they have a markedly increased extracellular fluid volume.

DR. CRAIG.—What about their total cardiac output?

DR. METCOFF.—Those measurements that have been made have all been normal.

DR. CRAIG.—I have always been impressed by the increases in heart size and weight in children dying with the nephrotic syndrome, even when the course was short and did not terminate in uremia. This child, too, had a large heart weighing about 50 per cent over the normal for the age. I have never been able to give satisfactory reasons for this increase in size, though anemia may certainly have a role in its production.

The kidneys were small and rather surprisingly so, weighing but 25 grams apiece. There were marked thickening, fibrosis, and chronic inflammation in the pelvis of both kidneys, but aside from frequent areas of interstitial inflammation, other evidences of chronic pyelonephritis were not seen. The majority of the glomeruli (Fig. 1) were markedly scarred. A few glomerular crescents were found, and even in the least involved glomerular tufts, thickening of the basement membrane was found after staining with the periodic and Schiff method. These changes are then consistent with chronic glomerulonephritis and a moderate degree of a superimposed pyelonephritis.

Fig. 1.

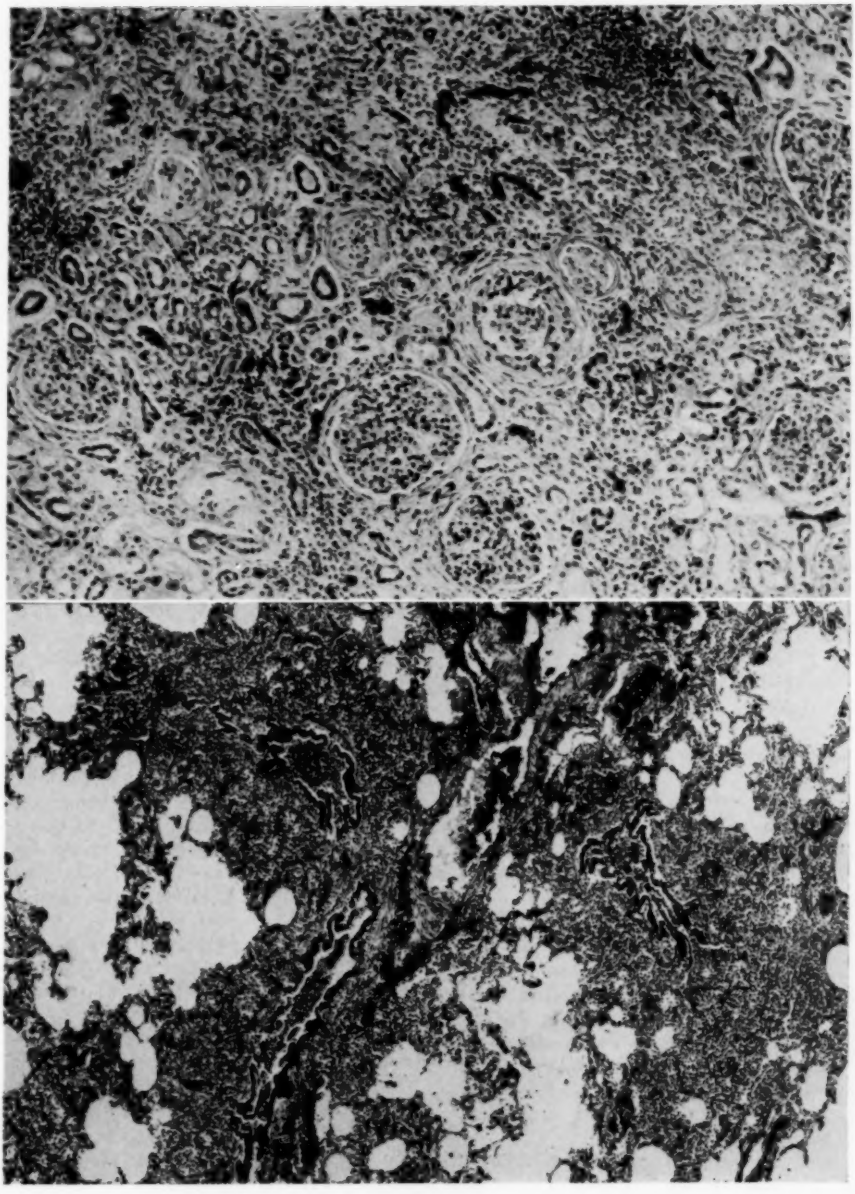


Fig. 2.

Fig. 1.—Kidney. There is marked scarring and atrophy of the glomeruli. Occasional crescents are seen. Increased interstitial inflammation is present. (Hematoxylin and eosin; ×110.)

Fig. 2.—Lung. A well-established bronchopneumonia is present. (Hematoxylin and eosin; ×90.)

The parathyroid glands were all enlarged, measuring up to 0.5 cm. in greatest diameter, yet the bones showed little evidence of osteitis fibrosa cystica, which is doubly surprising in view of the marked alterations in the serum chemical values for calcium and phosphorus. This lack of structural alteration in the bone may in part be due to the failure of growth which this child displaced. The child also had a rather severe and classical bronchopneumonia (Fig. 2); a *Staphylococcus aureus* was isolated at post mortem from the lung. In the bowel, although no actual bleeding points were detected, there were numerous hemosiderin deposits in the lamina propria of the small intestine. In view of the marked renal atrophy, I would favor Dr. Metcoff's interpretation of the onset of this child's illness with an acute glomerulonephritis, rather than Dr. Gitlin's, although certainly from the histological findings in the kidney one cannot say with any certainty which was the actual course of events.

REFERENCES

1. Gitlin, D., Janeway, C. A., and Farr, L. E.: Studies on the Metabolism of Plasma Proteins in the Nephrotic Syndrome. I. Albumin, Gamma Globulin, and Iron Binding Globulin, J. Clin. Invest. 35: 44, 1956.
2. Peters, J. P.: Edema of Acute Nephritis, Am. J. Med. 14: 498, 1953.
3. Eder, H. A., Lawson, H. P., Chinard, F. P., Greif, R. L., Cotzias, G. C., and Van Slyke, D. D.: A Study of the Mechanisms of Edema Formation in Patients With the Nephrotic Syndrome, J. Clin. Invest. 33: 636, 1954.

Comments on Current Literature

CHROMOGENIC ACID-FAST BACILLI FROM HUMAN SUBJECTS

INCLUDED among the large number of atypical tubercle bacilli and other acid-fast organisms isolated from human sources are certain chromogenic strains which have been recovered from patients with symptoms and roentgenographic findings simulating tuberculosis. A series of very informative papers concerning these chromogenic strains was prepared in 1951 by Tarshis and Frisch,[1] and appeared in the *American Review of Tuberculosis* for March, 1952. Despite the ubiquity of saprophytic mycobacteria, and the possible variants among acid-fast bacilli encountered in cultural studies, these authors concluded that the chromogenic acid-fast bacilli isolated from patients could be differentiated on cultural grounds alone from the saprophytic organisms. While the chromogens studied varied widely in their growth requirements, they did resemble tubercle bacilli in that they grew best and most typically on media which are standard for culturing *Mycobacterium tuberculosis*. The cultural characteristics observed, however, were considered sufficiently distinctive to be helpful in the differentiation of the three groups of organisms: the group associated with tuberculosis, the saprophytic group, and the chromogenic group of acid-fast bacilli.

In addition to cultural differences, observations in experimental animals, principally guinea pigs, indicated that the chromogenic bacilli produce a tuberculoid reaction, and that this infection in guinea pigs differs in a number of ways from the tuberculous infection of this animal, i.e., with *Myco. tuberculosis*. A striking feature of the pathogenesis was the tendency for the chromogenic strains to produce areas of central necrosis with abscess formation surrounded by polymorphous granulation tissue. The majority of strains studied did not result in progressive disease in the guinea pig, and healing was manifest as granulation proceeded to scar formation. Cross-immunization studies indicated an immunologic relationship between human tubercle bacilli and chromogenic acid-fast organisms; however, while they share antigenic properties, the two groups also have specific component characteristics of their own. On the basis of the experimental data accumulated, Tarshis and Frisch[1] expressed the view that "the chromogens occupy a position midway between the mammalian and saprophytic groups of mycobacteria." Such fundamental studies concerning the classification of acid-fast organisms isolated from human subjects are of great interest from the clinical point of view. At the same time they present many aspects which are confusing and need clarification.

A recent issue of the *Canadian Medical Association Journal* (Nov. 15, 1956) carries an interesting report by Prissick and Masson[2] entitled "Cervical Lymphadenitis in Children Caused by Chromogenic Mycobacteria." This report which comes from the Montreal Children's Hospital and the Department of Bacteriology and Immunology, McGill University, Montreal, is based on a study of fourteen strains of chromogenic acid-fast and alcohol-fast mycobacteria. Ten of these strains were obtained in pure culture from

pus aspirated from suppurating facial, submaxillary, or cervical lymph nodes in children in whom the clinical picture suggested tuberculous infection. This group of patients, who presented signs and symptoms of lymphadenitis, is of particular interest to the clinician. Pus obtained from suppurative lesions by clean aspiration yielded acid-fast chromogenic mycobacteria on culture. In two instances, the children, a girl of 18 months and a boy of 3 years, had received BCG at birth. The 18-month-old child had a dark red, preauricular swelling for five months from which pus could be aspirated. Yellow pigmented colonies of acid-fast and alcohol-fast rods grew on Löwenstein's medium at 37° C. The 3-year-old patient had seemed in very good health until three months before admission, when he developed a painless, soft mass on the right side of the neck. Aspirated pus yielded acid-fast rods, seen on direct smear of the material, and growing slowly on Löwenstein's medium (37° C.), with the production of yellow pigmented colonies. In this case, the patient not only had received BCG at birth, but showed a positive patch test and a negative chest film, and no family history of tuberculosis could be elicited. An epidemiologic picture even more confusing was presented by a boy, 2 years of age, who had adenitis of a subacute type, but who also had been exposed to his own father suffering from active tuberculosis. Material aspirated from the suppurative lymph nodes of this child yielded bright yellow colonies when cultured on Löwenstein's medium. Guinea pigs inoculated with this material showed no evidence of lesions over an observation period of three months. However, an excised node from this patient, submitted for detailed histologic study, was described as showing changes compatible with those of tuberculous infection.

In all ten of the patients with suppurating lymph nodes, aspirated material yielded chromogenic acid-fast bacteria on culture. In addition, chromogenic acid-fast organisms were isolated from pus aspirated from the pleural cavity—two patients, both adult males. The first of these patients had suffered from a chronic cough and experienced persistent loss of weight for five months. Empyema of the left chest was treated by surgical drainage; biopsy revealed no histologic evidence of tuberculosis or of malignant disease. The patient improved following drainage and was discharged. In the second instance, an adult male was being treated for staphylococcal empyema. Acid-fast organisms had not been identified on direct smear; however, simultaneous culture of the material on Löwenstein slopes yielded acid-fast rods in slowly growing, yellow-pigmented colonies. Since the patient improved on drainage and antibiotic therapy, this acid-fast organism was regarded as a contaminant.

In two other patients, strains of acid-fast mycobacteria were isolated from open lesions: in a child showing negative tuberculin reaction, bronchial fluid obtained at bronchoscopy yielded acid-fast rods growing in deep orange-yellow rough colonies on media standard for the isolation of *Myco. tuberculosis.* The second of these patients was a girl, 9 years of age, who had known exposure to active tuberculosis in her father. Tuberculin test in this child was positive, and joint and chest x-ray findings were suggestive of tuberculosis. Tissue scrapings from a joint lesion were cultured on various media; acid-fast rods growing in the typical yellow colonies of the chromogens appeared in the cultures, and also the characteristic deep gold, rough colonies of *Myco. tuberculosis.*

In addition to the original fourteen strains investigated, Prissick and Masson describe fifteen other strains apparently very similar, all of which were recovered from facial or cervical lymph nodes. Detailed histologic studies of resected lymph nodes were carried out in many instances. In the case of eight children, the histopathology of the affected nodes could

not be differentiated from that observed in tuberculosis. Tubercle formation, necrosis, caseation, granulation tissue, scarring, and calcification were seen, depending on the stage of the process. Attempts were made to evaluate the pathogenicity of the various strains by animal inoculation. In general, the chromogenic mycobacteria "differ in their pathogenic behavior from *Myco. tuberculosis* in not causing progressive disease and by their lack of tendency to produce ulcerative lesions in patients as in experimental animals."[2] A more detailed account of the morphology, and the cultural and biological characteristics of the various strains will be published in the near future.[3]

The unusual strains of chromogenic acid-fast mycobacteria isolated from human subjects have aroused considerable interest in both microbiological and clinical circles. The question has been raised as to whether such organisms are being isolated more frequently from patients who have received streptomycin. In the current report typical chromogenic strains were recovered from patients who had never received this drug. While the etiological importance of these acid-fast organisms must of necessity await further study, the recovery of ten strains, falling into the group of the chromogenic acid-fast bacilli, from suppurative closed lesions occurring in human subjects suggests clinical significance. Their acid-fast and alcohol-fast properties would place them in the order, Actinomycetales, an order which includes the family Mycobacteriaceae and the family Actinomycetaceae. Their morphology and staining reactions would suggest that the chromogenic mycobacteria belong to the Mycobacteriaceae. They differ from *Nocardia asteroides* and *N. intracellularis* in several distinct ways, and from *Myco. tuberculosis*, var. *hominis*, in at least one of the following characteristics: "ability to grow at room temperature, resistance to heat, resistance to para-aminosalicylic acid, and the ability to utilize paraffin as a sole source of carbon."[2]

Possible explanations for these chromogenic strains are discussed. That they might be variants of *Myco. tuberculosis*, var. *avium*, was suggested; however, none of the studies carried out by the current authors supports this conclusion. The possibility that these organisms are members of a saprophytic group of mycobacteria, such as those present normally in certain parts of the body, *Mycobacterium smegmatis* in urine, or various forms ingested with food which may be present in gastric juice, was considered. Repeated isolation of these chromogenic strains from pus aspirated from closed abscess cavities of cervical adenitis would seem to make this explanation unlikely. In one case only, that of the suppurative knee joint in a 9-year-old child, was there a mixture of acid-fast forms, *Myco. tuberculosis*, and a chromogenic strain. In all other instances the chromogenic strain was isolated in pure culture. The strains isolated from the ten children with subacute lymphadenitis were shown to have low-grade pathogenicity in experimental animals as well. Inoculation of large numbers of these organisms into guinea pigs produced slowly developing lesions which persisted for months, but did not give rise to progressive disease. Neither in patients, nor in experimental animals, did the lesions become ulcerative. As a result of their studies, the authors suggest that these chromogenic strains of acid-fast and alcohol-fast bacteria differ sufficiently from the nocardia and the mycobacteria with which they were compared to be classified separately, and propose the name *Mycobacterium scrofulaceum*.

The recent upsurge of interest in the study and treatment of tuberculosis will lead undoubtedly to improved understanding of the mycobacterium group of organisms and

their role in the etiology of clinical disease manifestations in human subjects. Further studies, presently in progress, concerning their cultural, antigenic, and sensitivity behavior, have been designed to evaluate, so far as is possible, the relationships of the various members of this group. The interesting series of patients, currently reported by Prissick and Masson,[3] in which low-grade lymphadenitis caused by chromogenic acid-fast bacteria was observed in children, emphasizes the complex nature of acid-fast infection in the human subject.

RUSSELL J. BLATTNER

REFERENCES

1. Tarshis, M. S., and Frisch, A. W.: Chromogenic Acid-Fast Bacilli From Human Sources: I. Cultural Studies, Am. Rev. Tuberc. **65**: 278, 1952; Ibid. II. Pathologic Studies, Am. Rev. Tuberc. **65**: 289, 1952; Ibid. III. Hypersensitivity Studies, Am. Rev. Tuberc. **65**: 302, 1952.
2. Prissick, F. H., and Masson, A. M.: A Preliminary Report on a Study of Pigmented Mycobacteria, Abstract, Annual Meeting, Canadian Public Health Association, Toronto, Dec. 17-18, 1951, Canad. J. Pub. Health **43**: 34, 1952.
   Cervical Lymphadenitis in Children Caused by Chromogenic Mycobacteria, Canad. M. A. J. **75**: 798, 1956.
3. Prissick, F. H., and Masson, A. M.: Canad. J. Microbiology, Feb., 1957, in press.

Correspondence

To the Editor:

We have read with interest Dr. John K. Wilson's case report of a 4-year-old boy in acute barbiturate poisoning and the fine editorial comment of Drs. James N. Ettel-dorf and Robert A. Woodbury on the treatment of this condition.

Having treated many patients in profound barbiturate coma with excellent results, we wish to contribute some of our thoughts on the management of these patients.

To begin with, we believe that these patients should be cared for by a team made up of at least an internist and an anesthesiologist. The anesthesiologist is included because, by virtue of his daily experiences, he is well trained in the management of the narcotized patient.

The plan of treatment is governed by the condition of the patient's respiratory and circulatory systems and the depth of coma.

The stomach should be emptied and lavaged and some saline cathartic introduced into it. When stomach or Levin tubes are used to carry out these measures, a definite hazard of contaminating the patient's lungs with food, fluid or medication exists. We avoid this by intubating the esophagus with a large-bore esophageal tube (24 F for a 4-year-old child) which has an inflatable cuff at its distal end. When the cuff is inflated, all stomach contents or lavaging fluid can pass only through the tube. Thus, the pharynx remains uncontaminated. This technique has been previously described by us (*American Journal of Surgery*, October, 1955). Once the immediate danger of aspiration is over, the esophageal tube is replaced by a double lumen gastric tube to which intermittent suction is applied.

We are unequivocally opposed to the use of analeptics because we are certain that they are of no value and have seen severe deleterious effects following their use by other workers.

It is sheer folly to allow severe hypoxia to go uncorrected for the sole purpose of retaining it as a stimulus to respiration. Administration of adequate concentrations of oxygen should be started very early. A clear airway is of vital importance for the survival of the patient. Tracheostomy should be performed electively when the patient is expected to remain unconscious for a long time. It reduces dead space (especially important in children), facili-

tates tracheobronchial toilet, and guarantees a clear airway.

Aerosol therapy using detergents and bronchodilators should be used.

Intermittent positive pressure via an endotracheal tube is the most efficient emergency method of performing artificial respiration. Electrostimulation with the Reiter apparatus is very satisfactory for sustaining respirations because it produces a near normal pattern of breathing without altering intrapulmonary or intrapleural pressures. In addition, it increases muscle tonus and helps to maintain a normal blood pressure. Also, because the apparatus does not have to be close to the patient while in use, it does not interfere with general nursing and medical care.

Intravenous infusions containing dilute concentrations of vasopressors are employed to correct hypotension. Levophed is used when the hypotension is severe or fails to respond to Neo-Synephrine, our drug of choice. Blood transfusions are given for the correction of severe anemia or blood volume depletion.

An indwelling urethral catheter is inserted to keep the bladder empty, facilitate determinations of urinary output, and avoid repeated catheterizations.

Intravenous antibiotics are administered early to establish adequate blood levels.

The patient who is expected to remain unconscious for a long time is placed on a Stryker bed so that he can be turned with ease from the supine to the prone position and vice versa. Thus, pulmonary drainage is facilitated, pulmonary congestion is decreased, stagnation of blood is minimized, and nursing care to all parts of the body is made easy.

Finally, we wish to stress the necessity for constant medical care because there is always the danger in comatose patients that situations will suddenly arise, demanding the immediate attention of a physician qualified to manage the emergency. It is our practice, whenever we care for a patient in barbiturate coma, to have one member of the anesthesia department present in the hospital.

We have a short (5 minutes) colored film taken during the treatment of a patient in barbiturate coma which we will be happy to lend to any group.

DANTE BIZZARRI, M.D.
JOSEPH G. GIUFFRIDA, M.D.
Department of Anesthesiology
Columbus Hospital and
New York Medical College
New York, N. Y.

[Much of the above outline of the treatment of barbituric acid poisoning is similar to the discussion by Drs. Wilson and Etteldorf referred to in the letter. The most important difference is that Drs. Bizzarri and Giuffrida, anesthetists, advocate a positive pressure method of artificial respiration with an intratracheal tube, while Drs. Wilson and Etteldorf advocated the use of a respirator, a choice of methods rather than principle. To use the intratracheal tube requires the services of a competent anesthetist. *The Editor.*]

News and Notes

The following were certified by the **American Board of Pediatrics**, at the examination at St. Louis, Mo., Dec. 7, 8, and 9, 1956.

Dr. L. Clarke Aaronson, 1204 E. So. Temple, Salt Lake City, Utah.

Dr. Doris J. D. Adam, University of Texas, Medical Branch, Galveston, Texas.

Dr. Constantine Spiro Anast, University of Missouri School of Medicine, Columbia, Mo.

Dr. John Marion Babich, 2728 J St. Sacramento, Calif.

Dr. James A. Ball, 10801 Garland Rd. Dallas, Texas.

Dr. William Paul Barron, 707 N. Vine, Harrison, Ark.

Dr. Charles Binney II, 1720 Pennsylvania Ave., Harlingen, Texas.

Dr. Arr Nell Boelsche, Children's Hospital, Galveston, Texas.

Dr. Patricia Anne Brennan, 1617 Brentwood Blvd., Brentwood, Mo.

Dr. David James Buddrus, 6247 Brookside, Kansas City, Mo.

Dr. Ralph Chase, 234 W. Beauregard St., San Angelo, Texas.

Dr. Stuart Kenneth Cohan, 6425 Richmond Rd., Bellaire, Texas.

Dr. Howard Clement Comstock, 1031 E. Michigan, Lansing 12, Mich.

Dr. William Scott Conkling, Navasota Medical Center, Navasota, Texas.

Dr. Richard W. Crensman, 444 W. Flower St., Phoenix, Ariz.

Dr. Paul Ronald Crellin, 900 Delphinium Dr., Billings, Mont.

Dr. Robert K. Endres, 4619 E. 40th St., Tulsa, Okla.

Dr. Mary Ellen Haggard, University of Texas, Medical Branch, Galveston, Texas.

Dr. Robert Huff Hardie, 104 Sul Ross, Houston, Texas.

Dr. Mack J. Harris, 5604 Dorothy Way, San Diego, Calif.

Dr. Thomas Sharit Harris, 208 Garfield, Laramie, Wyo.

Dr. William Louis Hauptmann, 3027 N. Woodward, Royal Oak, Mich.

Dr. Douglas Cragun Heiner, University of Arkansas Medical Center, Little Rock, Ark.

Dr. Henry Schrader Heitman, 4245 Winbourne Ave., Baton Rouge, La.

Dr. David Hamilton James, Jr., 658 N. Perkins Rd., Memphis, Tenn.

Dr. Avner Kauffman, 8816 S. Blackstone Ave., Chicago 19, Ill.

Dr. Vermelle C. Kelly, Homer G. Phillips Hospital, St. Louis 13, Mo.

Dr. Peter La Forte, 37 Eighth Ave., Brooklyn, N. Y.

Dr. Roy William Laughmiller, Jr., Doctor's Bldg., Maryville, Tenn.

Dr. Jerome Edmund Maisel, 163 E. Rockaway Rd., Hewlett, N. Y.

Dr. Ceferino A. Méndez Polo, 2206 Marginal-Park Blvd., Santurce, Puerto Rico.

Dr. William Finley Moore, Jr., 1020 Kapiolani St., Honolulu 14, Hawaii.

Dr. Homer Erwin Nash, Jr., 3136 A Easton Ave., St. Louis 6, Mo.

Dr. Robert Louis Pavy, 510 St. Landry St., Lafayette, La.

Dr. Virginia H. Peden, 7431 Washington, University City 5, Mo.

Dr. Don C. Petersen, The Clinic, 529 E. 10th St., Long Beach, Calif.

Dr. Milam Bernard Pharo, 8215 Westchester, Dallas, Texas.

Dr. Mary Barbara Scheurich, 212 S. 11th St., LaCrosse, Wis.

Dr. Patricia T. Schloesser, 1901 Collins, Topeka, Kan.

Dr. Edwin Collier Shepherd, 30 E. 60th St., Savannah, Ga.

Dr. Henry L. Sherrod, Jr., 1117 S. 22nd St., Birmingham, Ala.

Dr. Dorothy I. Smith, 42nd and Dewey Ave., Omaha, Neb.

Dr. David L. Sparling, Box 496, Mt. Edgecumbe, Alaska.

Dr. Benjamin Jennings Stone, 1031 E. Michigan Ave., Lansing 12, Mich.

Dr. Thomas Edward Townsend, 1310 Cherry St., Pine Bluff, Ark.

Dr. Stephan B. Van Adelsberg, 3875 Wilshire Blvd., Los Angeles 5, Calif.

Dr. Lester Wishingrad, 8563 S. Woodlawn, Chicago, Ill.

Dr. Casper E. Wiggins, Medical Arts Bldg., Greenwood, S. C.

Special Foreign Certificates:

Dr. Max Shein, Paseo de la Reforma 157-201, Mexico D. F., Mexico.

Dr. Seeta Sinclair, c/o Ernest A. Sinclair, Blodgett Memorial Hospital, Grand Rapids 6, Mich.

Dr. Gunnar B. Stickler, G. B. St. Garching/Alz, Obb., Germany.

The following listed diplomate was certified at New York City, October 13, 1956, and will receive a *Special Foreign Certificate*

Dr. Hilda Feng-Kai Lin, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York, N. Y.

Dr. Stanley Gibson of Chicago died October 24, 1956. He was Professor Emeritus of Pediatrics at Northwestern University Medical School, a member of the American Pediatric Society and the American Academy of Pediatrics. For many years he was connected with the Children's Memorial Hospital in Chicago.

Dr. C. Henry Kempe, formerly Assistant Professor of Pediatrics at the University of California School of Medicine, has been appointed Professor of Pediatrics and Head of the Department at the University of Colorado School of Medicine at Denver.

The **Intermountain Pediatric Society** will hold its annual clinical convention at the Hotel Riviera, Las Vegas, Nevada, March 18 and 19. Guest speakers will include Dr. Sidney Gellis, Boston, Mass.; Dr. James Wilson, Ann Arbor, Mich.; Dr. John A. Anderson, Minneapolis, Minn. The meeting is open to all physicians. For further information write Intermountain Pediatric Society, 2000 S. 1300 East, Salt Lake City 5, Utah.

The **Second Inter-American Medical Convention** will convene at the Hotel El Panama, Panama City, Republic of Panama, April 3, 4 and 5, 1957, under the sponsorship of the Medical Society of the Isthmian Canal Zone, a chapter of the American Medical Association since 1906. Colonel Charles O. Bruce, MC, USA, Chief Health Officer of the Panama Canal Company and President of the Medical Society, will act as keynote speaker at the invocation ceremonies, which will include addresses by the President of the Republic of Panama and by the Governor of the Panama Canal Zone. For further information write to Dr. William T. Bailey, Chairman of the Convention Executive Committee, Gorgas Hospital, Ancon, Panama Canal Zone.

A practical approach to pediatric problems has been planned for the annual *Postgraduate Course in Pediatrics*, to be held March 11, 12 and 13, at the **University of Kansas Medical Center**, Kansas City, Kansas. As in previous years, the utilization of available case material will be one of the high lights of the program. The guest faculty includes a number of nationally recognized teachers and clinicians in the field of pediatrics. Information concerning details of the program, registration, etc., may be obtained by writing to the Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 12, Kansas.

Harvard Medical School announces the following *Post-Graduate Courses in Pediatrics:*

1. Pediatrics 3—June 3 to 14, inclusive, 1957; daily 9:15 A.M. to 4:30 P.M., Massachusetts General Hospital. This course provides a general review with emphasis on recent advances and therapy. The first seven days will be devoted to pediatric, medical, surgical, orthopedic, cardiac, allergic, dermatologic, psychiatric, eye, ear, and x-ray problems. The last four days will be

concentrated on disorders of growth and development, common endocrine problems, and the metabolic aspects of infant feeding, parenteral fluid therapy, and management of nephritic and diabetic patients.

2. Pediatric Metabolism and Endocrinology—June 11 to 14, inclusive, 1957; daily 9:15 A.M. to 4:30 P. M., Massachusetts General Hospital. This course is the same as the last four days of Pediatrics 3 as described above, but may be taken separately.

Those interested should write: Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston Mass.

The following teaching program will be given in 1957 by the **International Children's Centre:**

I. *Course on School Health Problems* (for school welfare workers) Jan. 15-Feb. 10, 1957.

The course will bring together for about a month thirty students from various countries, who will be called upon to take an active share in the teaching and to set forth for the benefit of their colleagues, in the course of study circles and discussions, the present state and the trends of school health work in their respective countries.

II. *Course on Social Pediatrics* (for physicians) April 8-July 1, 1957.

This tenth course of Social Pediatrics is intended for physicians, either pediatricians or health officials in charge of organizing MCW. The program will include all the major problems of medical social action on behalf of childhood. It will last three months and it will take place partly in France and partly out of France (Poland, Czechoslovakia). It is to be attended by thirty participants from twenty-five countries.

III. *Training Course for Teams in Charge of Rearing Premature Infants.*

This practical training course arranged by the International Children's Centre in cooperation with the World Health Organization (Regional Office for Europe) takes place at the Centre for Premature Infants of the School of Child Care of the Paris Faculty of Medicine (Professor Marcel Lelong).

The training of pediatricians is to last for at least one month, that of child care nurses for at least three months.

IV. *Practical Training Course for Personnel in Charge of the Rehabilitation of Children Affected With Motor Disabilities* (for kinesitherapists) October 1, 1956-March 1, 1957.

This training course has been arranged by the International Children's Centre in agreement with the Medical Direction and the Administrative Direction of the Rehabilitation Centre Raymond Poincaré in Garches where it will take place. The students will share in the work and the daily routine of the permanent staff of the Centre.

The number of scholarships granted by the ICC for this training course is limited to eight.

V. *Course on Problems of Mother and Child Welfare* (for welfare and administrative personnel) Oct. 7-Dec. 14, 1957.

This course is intended for both welfare and administrative personnel. Special emphasis is to be given to matters pertaining to organization and administrative implementation, as well as to coordination and teamwork.

Two study journeys are provided for: one to the Public Health Centre of Soissons (a fortnight), the other to the Office of Social Health of Meurthe and Moselle (one week).

VI. *Course on the Prevention of Tuberculosis* (in English).

As in previous years, the International Children's Centre will participate in the 1957 course arranged for oversea students by Professor Heaf, Department of Tuberculosis, University of Wales, Cardiff.

Physicians from English-speaking countries may attend the course as unsponsored students.

VII. *Training Course for Health Administrators and Directors of Rehabilitation Centres* (motor disabilities).

In response to a wish expressed by members of its Technical Advisory Committee, the International Children's Centre proposes to arrange a training course for health administrators and directors of rehabilitation centres sometime next Spring.

The number of participants is to be limited to six.

For additional information, apply to: Public Relations Service, Château de Longchamp, Bois de Boulogne, Paris-XVI.•

Books

Cardiac Diagnosis. R. F. Rushmer, M.D., Philadelphia, 1956, W. B. Saunders Co., 447 pages. Price $11.50.

This book is divided into five parts. Part I and Part II describe the function and regulation of the normal cardiovascular system. Part III is a discussion of cardiac reserve and the etiology of congestive failure. Part IV reviews the methods of cardiac diagnosis, and Part V very briefly discusses myocardial ischemia, myocarditis, valvular disease, and congenital heart disease.

The first four parts represent excellent, simplified, concise reviews pertaining to the function and regulation of the cardiovascular system and is supported by many excellent diagrams which represent a wonderful review of the fundamental principles of physiology of the cardiovascular system for the clinician. In the same sections Dr. Rushmer includes a good portion of his original work on the mechanism of ventricular ejection and the regulation of cardiac output. One is continually fascinated by the ingenious electronic devices described by the author in developing his studies. Part V, which is entitled "Diagnosis of Cardiac Disease," is somewhat weak because it merely represents a very brief review on the subject of organic heart disease.

The book is recommended very highly as reading matter for the pediatrician and internist whose subspecialty is cardiology.

When Your Child Is Ill. Samuel Karelitz, M.D., New York, 1957, Simon and Schuster, 490 pages. Price $4.95.

Dr. Karelitz has written a book for parents that will furnish them with a lot of sound medical knowledge. Moreover, it is the type of a lay medical text that the physician can wholeheartedly recommend without reservation. It has its basis on a broad, practical knowledge of what the parent wants to know, combined with sound scientific knowledge upon which the answers are based. The author has divided diseases for the text into five general headings, and includes an introductory section "About Causes, Symptoms, and Methods" in which allergy, viruses, fever, the "wonder drugs," immunization, and hygiene are discussed. Under the diseases some 39 specific conditions are taken up, ranging from chicken pox to fungous infections. Each condition is discussed in as nontechnical language as is possible, and then comes a question and answer section. Every experienced practitioner will find many old friends he has been asked again and again, and spent hours in answering. We should say the author has a batting average of about 99 per cent in his answers—a much higher average than might be expected. The practitioner will find it a most useful book to recommend to parents, and it will undoubtedly be used to save him a tremendous amount of his time. It ends with a glossary of terms that cannot be avoided in a medical text.

Clinical Examinations in Neurology. Sections of Neurology and Physiology, Mayo Clinic and Foundation, Philadelphia, 1956, W. B. Saunders Co., 370 pages.

A text prepared by the physicians of the Section of Neurology and Physiology of the Mayo Clinic. Some fourteen members of the staff have contributed to the volume although the individual contribution is not listed. It is a practical text going into the history and record forms as well as detailed discussion of the examination procedure. Among these are discussions of the cranial nerve, motor function, reflexes, mental function, electroencephalography, cerebrospinal fluid, etc.

La salud del hijo. Puericultura. Juan P. Garrahan, Buenos Aires, 1955, Libreria "El Ateneo," 603 pages.

In the first part of the text Professor Garrahan discusses the normal infant and child, infant feeding, growth and development, and education. The second part is concerned with his illnesses and diseases.

Low-Fat Cookery. Evelyn S. Stead and Gloria K. Warren, New York, 1956, McGraw-Hill Book Co., 184 pages. Price $3.95.

A recipe book containing many tested recipes for foods low in fats. Both authors are married to professors in the medical department of the Duke School of Medicine.

Editor's Column

"THE STORY OF ASPIRIN"

[Last November the Monsanto Chemical Company held a symposium on aspirin research, celebrating the production that month of their 100 millionth pound of aspirin. At a dinner between sessions Dr. Carroll Hochwalt, Vice President for Research and Development, told "The Story of Aspirin." It was of so much interest to the physicians present that with Dr. Hochwalt's kind permission we quote from his remarks.]

Nothing could better exemplify that collaborative bond between the test tube and the stethoscope than does the colorful history of the compounds which are under discussion today in this symposium. Hippocrates himself, you may know, prescribed a salicylate when he recommended willow bark as a painkiller more than 2,300 years ago. Slightly more than 100 years ago, the German chemist Hermann Kolbe made chemical history when he successfully synthesized salicylic acid. And, in the grand tradition of chemistry, he gave to medicine an effective palliative and antipyretic while looking for something else!

The story begins a bit earlier than that, however, with a Glasgow surgeon named Lister who learned of the disinfecting properties of carbolic acid and began using it in antisepsis. After he had succeeded in saving the life of Queen Victoria by liberal applications of carbolic acid to her surgical wound, the practice gained in popularity with surgeons. No report is available on the reaction of patients but, knowing the potency of the compound, we can assume that they responded actively to the therapy!

Carbolic acid (which we know as phenol) was just too strong an acid for the liberal medical use which was pioneered and practiced by Lister. In Germany, a surgeon who hoped to find some way of using carbolic acid *internally* on his patients to combat their diseases took the problem to Hermann Kolbe, professor of chemistry at the University of Leipzig. This was in the 1870's.

Kolbe figured that he had just the answer. He recalled how, twenty years earlier, he had succeeded in synthesizing salicylic acid from carbolic acid and the fact that it slowly broke down in the test tube and became carbolic acid again. Surely it would do the same thing in the human body and thus kill off the disease germs.

Fired with the idea of perfecting a germ-killing successor to carbolic acid, Kolbe busily perfected a commercially practical synthesis for salicylic acid by reacting carbon dioxide with sodium phenate under heat and pressure. (A process, by the way, which still is in use today with but minor refinements.) His assistants tested the compound crudely on a variety of microbes and bacteria and obtained encouraging results. When the news was made public in 1874, doctors clamored for the new salicylic acid "germ killer" and its use spread rapidly. It was applied liberally to cuts and wounds (where it actually did promote healing) and also was administered internally for any and every kind of disease. It was even

taken up by food manufacturers and used as a preservative in their products. Kolbe was so confident of his new "germ killer" that he is reported to have encouraged one of his students to go into business with a small salicylic acid plant. The student's name was Heyden and you may have heard of his chemical company.

Within a year, however, doctors bebegan reporting the fact that dosages of the salicylic acid, while seeming to help their patients, did not really effect any cures. It would reduce their fevers and relieve their pains but it failed to stem the diseases or their fatal toll.

A young Swiss physician named Carl Buss pondered carefully over the bewildering performance of the drug. Victims of typhoid, pneumonia, and all of the other diseases responded similarly to salicylic acid. Whatever the cause of their fevers, the compound promptly and dramatically reduced them.

Then, from Berlin's Dr. Franz Stricker came the further report that salicylic acid not only reduced fever but relieved the pain and swollen joints of rheumatism. Following these came more reports confirming the compound's palliative effect not only for the rheumatic and diseased but for those suffering the pains of neuritis, neuralgia, and headaches.

Hermann Kolbe had failed to find the germ killer which his theory had predicted; he had found only an effective, economical and easily obtainable antipyretic, analgesic, and antirheumatic!

Heyden's salicylic acid plant in Dresden was doing a capacity business as demand soared for the compound. At Düsseldorf, the order of the day for Friedrich Bayer and Company's chemists was to find a compound competitively superior to Heyden's. And there was room for improvement, too, for salicylic acid frequently produced nausea and other symptoms almost as discomforting as the pains which it was to relieve.

A young staff chemist at Bayer named Felix Hoffmann had another good reason for seeking a successor compound in addition to his employer's orders. His father was racked with pains of rheumatoid arthritis and desperate for a palliative which would be less irritating than his salicylic acid.

Hoffmann searched for likely compounds among the records of chemical oddities and misfits and, there, ran across acetylsalicylic acid. The compound had been discovered in 1853 by Charles Frederic von Gerhardt who had reported it as a novel but useless derivative and abandoned it to a 46-year obscurity until Hoffmann's chance encounter of it.

Heinrich Dreser was director of Bayer's pharmacological research and a scientist of great prominence in Europe. Hoffmann prepared samples of pure acetylsalicylic acid, tested them in the laboratory and on his long-suffering father, and, convinced that he had something, laid the compound and his data before *Herr Doktor*.

Dreser's clinical evaluation of the compound proved it to be outstanding in all respects. Only one thing was wrong with it: its chemical name was hard to pronounce and sounded entirely too much like the salicylic acid it would have to meet and beat in the market place. But Dreser remembered that natural salicylic acid originally had been extracted from plants of the spirea family and, for that reason, was known also as spiric acid or *spirin*. He added the "a" from acetyl to the latter and coined the name for Bayer's newest drug: Aspirin.

Carefully protected by patents, Bayer enjoyed an immensely profitable seventeen years of world monopoly in aspirin sales, marred only by the occasional infringement of entrepreneurs who could not resist the temptation to risk a little bootlegging of acetylsalicylic acid into the channels of pharmacy.

During the forty-year period dating from Kolbe's commercial synthesis of salicylic acid in 1874 to the eve

of World War I, Germany held a virtual world monopoly in synthetic drugs and in the intermediate chemicals necessary for their manufacture. It was an era of pharmaceutical discovery dominated by such palliatives as the salicylates, antipyrine, antifebrin, phenacetin, and, last and best, aspirin.

Bayer's United States patent on aspirin expired on February 27, 1917. Monsanto and other American chemical companies had plant facilities for aspirin in readiness for this expiration. Little more than a month later, in April, 1917, Monsanto became the first independent producer of aspirin in the United States, joined shortly thereafter by several other chemical companies.

Late in 1912, Dr. Gaston DuBois of Monsanto had visited a prominent chemist in Switzerland and purchased from him, for 2,000 Swiss francs, a process for making pure acetylsalicylic acid in one operation. After a thorough test out of the process, Monsanto built a plant for the process in 1916. The company produced and sold 2,368 pounds of the product in 1917.

The Bayer Company fought hard both before and after its patent expiration to reserve for itself exclusively the use of the name "aspirin" for acetylsalicylic acid. The company claimed that Dr. Dreser's cleverly coined name for the product was a trademark of Bayer and that, while anyone could make aspirin following the patent expiration, only the production of Bayer could be called by that name.

This led to considerable pamphleteering, editorializing, and court-fighting by parties on both sides of the issue with Mr. Queeny [Founder of Monsanto] strongly leading the opposition to Bayer's view. In November, 1918, the Patent Office cancelled Bayer's registered rights to the name as having been improperly and unlawfully registered. The last hurdle had been cleared, and U. S. chemical producers definitely were in the aspirin business. Monsanto's production rose in 1919 to 480,874 pounds.

There still is much to be learned, I understand, of the compound's mechanisms of action. How does it do what it does for the rheumatic and arthritic sufferers? Why does it reduce abnormal body temperatures while having no effect upon normal temperatures? Just what is the means by which aspirin succeeds in moderating pain? The answers to these questions are sure to come in time, I believe, and with them may come still more important applications for this cheapest, safest, and most perennially durable of the genuine "wonder" drugs.